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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	8449-123-999	Total Pages	25
First Named Inventor or Application Identifier			
Pramod K. Srivastava			
Express Mail Label No.	EL 501 633 351 US		

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

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2. <input checked="" type="checkbox"/> Specification <i>(83 specification + 2 Table of Contents) (preferred arrangement set forth below)</i>	7. <input checked="" type="checkbox"/> Nucleotide and/or Amino Acid Sequence Submission <i>(if applicable, all necessary)</i>
<ul style="list-style-type: none"> -Descriptive title of the Invention -Cross Reference to Related Applications -Statement Regarding Fed sponsored R&D -Reference to Microfiche Appendix -Background of the Invention -Brief Summary of the Invention -Brief Description of the Drawings <i>(if filed)</i> -Detailed Description of the Invention (including drawings, <i>if filed</i>) -Claim(s) -Abstract of the Disclosure 	
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5. <input type="checkbox"/> Incorporation By Reference <i>(useable if Box 4b is checked)</i> The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.	10. <input type="checkbox"/> English Translation Document <i>(if applicable)</i>
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Pramod K. Srivastava

Application No.: Not yet assigned

Group Art Unit: Not yet assigned

Filed: July 25, 2000

Examiner: Not yet assigned

For: ALPHA (2) MACROGLOBULIN RECEPTOR AS A
HEAT SHOCK PROTEIN RECEPTOR AND USES
THEREOF

Attorney Docket No.: 8449-123-999

**TRANSMITTAL OF VERIFIED STATEMENTS AND
REQUEST TO ESTABLISH SMALL ENTITY STATUS**

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

The Applicant submits herewith the following documents for the above-mentioned application: (1) a Verified Statement Claiming Small Entity Status for the University of Connecticut Health Center; and (2) a Verified Statement Claiming Small Entity Status for Antigenics, LLC.

The Applicant has assigned his entire right, title and interest in the instant application to the University of Connecticut Health Center. The University of Connecticut Health Center has granted certain rights in the application to Antigenics, LLC. The University of Connecticut qualifies as a Small Entity under 37 C.F.R. §§ 1.9(f) and 1.27(d). Antigenics, LLC qualifies as a Small Entity under 37 C.F.R. §§ 1.9(f) and 1.27(c).

It is respectfully requested that the application be accorded Small Entity Status in accordance with 37 C.F.R. §§ 1.9(f), 1.27(c) and 1.27(d). Please charge the required fee to Pennie & Edmonds LLP Deposit Account No. 16-1150. A duplicate of this sheet is enclosed for accounting purposes.

Respectfully submitted,

Date: July 25, 2000

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Enclosures

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Application of: Pramod K. Srivastava

Application No.: To be assigned
 Patent No.:

Group Art Unit: To be assigned

Filed: herewith
 Issued:

Examiner: To be assigned

For: ALPHA (2) MACROGLOBULIN RECEPTOR
AS A HEAT SHOCK PROTEIN RECEPTOR
AND USES THEREOF

Attorney Docket No.: 8449-123-999

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
[37 CFR 1.9(f) and 1.27(c)] - Small Business Concern

Assistant Commissioner for Patents
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Sir:

I hereby declare that I am

the owner of the small business concern identified below:
 an official of the small business concern empowered to act in behalf of
the concern identified below:

Name of organization Antigenics, LLC
Address of organization 630 Fifth Avenue, Suite 2100
New York, NY 10111

I hereby declare that the above identified small business concern qualifies as a small business concern as defined in 37 CFR 1.9(d), for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the person employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern and/or there is an obligation under contract or law by the inventor(s) to convey rights to the small business concern with regard to the invention entitled "ALPHA (2) MACROGLOBULIN RECEPTOR AS A HEAT SHOCK PROTEIN RECEPTOR AND USES THEREOF", by inventor Pramod K. Srivastava, described in

the specification filed herewith
 application no. filed:
 patent no. issued

If the rights held by the above identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below and no rights to the invention are held by any person, other than the inventor, who could not qualify as an independent inventor under 37 CFR 1.9(c) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d), or a nonprofit organization under 37 CFR 1.9(e).

FULL NAME University of Connecticut Health Center
ADDRESS 263 Farmington Avenue
Farmington, Connecticut 06030
 INDIVIDUAL SMALL BUSINESS CONCERN NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. [37 CFR 1.28 (b)]

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, and patent issuing thereon, or any patent to which this verified statement is directed.

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Signature G. Armen Date 7-25-00

*NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities.
(37 CFR 1.27)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Application of: Pramod K. Srivastava
 Patent of:

Application No.: To be assigned
 Patent No.:

Group Art Unit: To be assigned

Filed: herewith
 Issued:

Examiner: To be assigned

For: ALPHA (2) MACROGLOBULIN
RECEPTOR AS A HEAT SHOCK PROTEIN
RECEPTOR AND USES THEREOF

Attorney Docket No.: 8449-123-999

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
[37 CFR 1.9(f) and 1.27(d)] - Nonprofit Organization

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I hereby declare that I am an official empowered to act on behalf of the nonprofit organization identified below:

Name of organization University of Connecticut Health Center
Address of organization 263 Farmington Avenue
Farmington, Connecticut 06030

Type of organization

University or other institution of higher education
 Tax exempt under Internal Revenue Service Code (26 USC 501(a) and 501(c)(3))
 Nonprofit scientific or educational under statute of state of the United States of America
(Name of state _____)
(Citation of statute _____)
 Would qualify as tax exempt under Internal Revenue Service Code (26 USC 501(a) and 501(c)(3)) if located in the United States of America.
 Would qualify as nonprofit scientific or educational under statute of state of the United States of America if located in the United States of America
(Name of state _____)
(Citation of statute _____)

I hereby declare that the nonprofit organization identified above qualifies as a nonprofit organization as defined in 37 CFR 1.9(e) for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code with regard to the invention entitled "ALPHA (2) MACROGLOBULIN RECEPTOR AS A HEAT SHOCK PROTEIN RECEPTOR AND USES THEREOF", by inventor Pramod K. Srivastava, described in

the specification filed herewith
 application no. filed:
 patent no. issued

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I hereby declare that rights under contract or law have been conveyed to and remain with the nonprofit organization identified above and/or there is an obligation under contract or law by the inventor(s) to convey rights to the nonprofit organization identified above with regard to the invention.

If the rights held by the nonprofit organization are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who could not qualify as an independent inventor under 37 CFR 1.9(c) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

FULL NAME Antigenics, LLC
ADDRESS 630 Fifth Avenue, Suite 2100
New York, NY 10111
 INDIVIDUAL SMALL BUSINESS CONCERN NONPROFIT
ORGANIZATION

FULL NAME _____
ADDRESS _____

 INDIVIDUAL SMALL BUSINESS CONCERN NONPROFIT
ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. [37 CFR 1.28 (b)]

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, and patent issuing thereon, or any patent to which this verified statement is directed.

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Signature Leonard P. Paplauskas Date 7/25/00

*NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities.
(37 CFR 1.27)

ALPHA (2) MACROGLOBULIN RECEPTOR AS A HEAT SHOCK PROTEIN
RECEPTOR AND USES THEREOF

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**ALPHA (2) MACROGLOBULIN RECEPTOR AS A HEAT SHOCK PROTEIN
RECEPTOR AND USES THEREOF**

5 This application claims priority under 35 U.S.C. § 119(e) to provisional application no. 60/209,095, filed June 2, 2000, which is incorporated by reference herein in its entirety. The invention was made with government support under grant number CA64394 awarded by the National Institutes of Health. The government has certain rights in the invention.

10 **1. INTRODUCTION**
The present invention relates to the use of alpha (2) macroglobulin ("α2M") receptor as a heat shock protein receptor, cells that express the α2M receptor bound to an HSP, and antibodies and other molecules that bind the α2M receptor-HSP complex. The invention 15 also relates to screening assays to identify compounds that modulate the interaction of an HSP with the α2M receptor, and methods for using compositions comprising α2M-receptor sequences for the diagnosis and treatment of immune disorders, proliferative disorders, and infectious diseases.

20 **2. BACKGROUND OF THE INVENTION**

2.1. HEAT SHOCK PROTEINS

Heat shock proteins (HSPs), also referred to as stress proteins, were first identified as proteins synthesized by cells in response to heat shock. Hsps have classified into five families, based on molecular weight, Hsp100, Hsp90, Hsp70, Hsp60, and smHsp. Many 25 members of these families were found subsequently to be induced in response to other stressful stimuli including nutrient deprivation, metabolic disruption, oxygen radicals, and infection with intracellular pathogens (see Welch, May 1993, *Scientific American* 56-64; Young, 1990, *Annu. Rev. Immunol.* 8:401-420; Craig, 1993, *Science* 260:1902-1903; Gething *et al.*, 1992, *Nature* 355:33-45; and Lindquist *et al.*, 1988, *Annu. Rev. Genetics* 30 22:631-677).

Heat shock proteins are among the most highly conserved proteins in existence. For example, DnaK, the Hsp70 from *E. coli* has about 50% amino acid sequence identity with Hsp70 proteins from excoriates (Bardwell *et al.*, 1984, *Proc. Natl. Acad. Sci.* 81:848-852). The Hsp60 and Hsp90 families also show similarly high levels of intra-family conservation 35 (Hickey *et al.*, 1989, *Mol. Cell. Biol.* 9:2615-2626; Jindal, 1989, *Mol. Cell. Biol.* 9:2279-

2283). In addition, it has been discovered that the Hsp60, Hsp70 and Hsp90 families are composed of proteins that are related to the stress proteins in sequence, for example, having greater than 35% amino acid identity, but whose expression levels are not altered by stress.

Studies on the cellular response to heat shock and other physiological stresses 5 revealed that the HSPs are involved not only in cellular protection against these adverse conditions, but also in essential biochemical and immunological processes in unstressed cells. HSPs accomplish different kinds of chaperoning functions. For example, members of the Hsp70 family, located in the cell cytoplasm, nucleus, mitochondria, or endoplasmic reticulum (Lindquist *et al.*, 1988, Ann. Rev. Genetics 22:631-677), are involved in the 10 presentation of antigens to the cells of the immune system, and are also involved in the transfer, folding and assembly of proteins in normal cells. HSPs are capable of binding proteins or peptides, and releasing the bound proteins or peptides in the presence of adenosine triphosphate (ATP) or low pH.

15 2.2. IMMUNOGENICITY OF HSP-PEPTIDE COMPLEXES

Srivastava *et al.* demonstrated immune response to methylcholanthrene-induced sarcomas of inbred mice (1988, Immunol. Today 9:78-83). In these studies, it was found that the molecules responsible for the individually distinct immunogenicity of these tumors were glycoproteins of 96kDa (gp96) and intracellular proteins of 84 to 86kDa (Srivastava *et* 20 *al.*, 1986, Proc. Natl. Acad. Sci. USA 83:3407-3411; Ullrich *et al.*, 1986, Proc. Natl. Acad. Sci. USA 83:3121-3125). Immunization of mice with gp96 or p84/86 isolated from a particular tumor rendered the mice immune to that particular tumor, but not to antigenically distinct tumors. Isolation and characterization of genes encoding gp96 and p84/86 revealed significant homology between them, and showed that gp96 and p84/86 were, respectively, 25 the endoplasmic reticular and cytosolic counterparts of the same heat shock proteins (Srivastava *et al.*, 1988, Immunogenetics 28:205-207; Srivastava *et al.*, 1991, Curr. Top. Microbiol. Immunol. 167:109-123). Further, Hsp70 was shown to elicit immunity to the tumor from which it was isolated but not to antigenically distinct tumors. However, Hsp70 depleted of peptides was found to lose its immunogenic activity (Udono and Srivastava, 30 1993, J. Exp. Med. 178:1391-1396). These observations suggested that the heat shock proteins are not immunogenic per se, but form noncovalent complexes with antigenic peptides, and the complexes can elicit specific immunity to the antigenic peptides (Srivastava, 1993, Adv. Cancer Res. 62:153-177; Udono *et al.*, 1994, J. Immunol., 152:5398-5403; Suto *et al.*, 1995, Science, 269:1585-1588).

35 Noncovalent complexes of HSPs and peptide, purified from cancer cells, can be used for the treatment and prevention of cancer and have been described in PCT publications WO

96/10411, dated April 11, 1996, and WO 97/10001, dated March 20, 1997 (U.S. Patent No. 5,750,119 issued April 12, 1998, and U.S. Patent No. 5,837,251 issued November 17, 1998, respectively, each of which is incorporated by reference herein in its entirety). The isolation and purification of stress protein-peptide complexes has been described, for example, from 5 pathogen-infected cells, and can be used for the treatment and prevention of infection caused by the pathogen, such as viruses, and other intracellular pathogens, including bacteria, protozoa, fungi and parasites (see, for example, PCT Publication WO 95/24923, dated September 21, 1995). Immunogenic stress protein-peptide complexes can also be prepared by in vitro complexing of stress protein and antigenic peptides, and the uses of such 10 complexes for the treatment and prevention of cancer and infectious diseases has been described in PCT publication WO 97/10000, dated March 20, 1997 (U.S. Patent No. 6,030,618 issued February 29, 2000. The use of stress protein-peptide complexes for sensitizing antigen presenting cells in vitro for use in adoptive immunotherapy is described in PCT publication WO 97/10002, dated March 20, 1997 (see also U.S. Patent No. 5,985,270 15 issued November 16, 1999).

2.3. ALPHA (2) MACROGLOBULIN RECEPTOR

The alpha (2) macroglobulin receptor (“ α 2MR”), also known as LDL (low-density lipoprotein) receptor-Related Protein (“LRP”) or CD91, is primarily expressed in liver, brain 20 and placenta. The α 2MR is a member of the low density lipoprotein receptor family. The extracellular domain of the human receptor comprises six 50-amino acid EGF repeats and 31 complement repeats of approximately 40-42 amino acids. The complement repeats are organized, from the amino to the carboxy-terminus, into clusters of 2, 8, 10 and 11 repeats, 25 called Cluster I, II, III and IV (Herz *et al.*, 1988, EMBO J. 7:4119-4127). One study points to Cluster II (Cl-II), which contains complement repeats 3-10 (CR3-10), as the major ligand binding portion of the receptor (Horn *et al.*, 1997, J. Biol. Chem. 272:13608-13613). The α 2M receptor plays a role in endocytosis of a diversity of ligands. In addition to α 2M, other 30 ligands of α 2MR include lipoprotein complexes, lactoferrin, tissue-type plasminogen activator (tPA), urokinase-type plasminogen activator (uPA), and exotoxins. Thus, the α 2M receptor plays roles in a variety of cellular processes, including endocytosis, antigen presentation, cholesterol regulation, ApoE-containing lipoprotein clearance, and chylomicron remnant removal.

Human α 2M is synthesized as a 1474 amino acid precursor, the first 23 of which 35 function as a signal sequence that is cleaved to yield a 1451 amino acid mature protein (Kan *et al.*, 1985, Proc. Natl. Acad. Sci. U.S.A. 82:2282-2286). In experiments with recombinant

protein, the carboxy-terminal 138 amino acids of α 2M (representing amino acids 1314-1451 of the mature protein) was found to bind the receptor. This domain has been called the RBD (receptor-binding domain; Salvesent *et al.*, 1992, FEBS Lett. 313:198-202; Holtet *et al.*, 1994, FEBS Lett. 344:242-246). An RBD variant (RBDv), a proteolytic fragment of α 2M comprising an additional 15 amino terminal residues (representing amino acids 1314-1451 of the mature protein) binds to the receptor with almost the same affinity as α 2M-proteinase (Holtet *et al.*, 1994, FEBS Lett. 344:242-246).

Alignment of α 2MR ligands identifies a conserved domain present in the RBDs of α macroglobulins. The conserved sequence spans amino acids 1366-1392 of human α 2M. 10 Conserved residues within this domain are Phe₁₃₆₆, Leu₁₃₆₉, Lys₁₃₇₀, Val₁₃₇₃, Lys₁₃₇₄, Glu₁₃₇₇, Val₁₃₈₂, Arg₁₃₈₄ (Nielsen *et al.*, 1996, J. Biol. Chem. 271:12909-12912). Of these, Lys₁₃₇₀ and Lys₁₃₇₄ were shown to be critical for receptor binding (Nielsen *et al.*, 1996, J. Biol. Chem. 271:12909-12912).

Binding of ligands, including the binding to α 2M, to α 2MR is inhibited by α 2MR-associated protein (RAP). RAP is a 39 kDa folding chaperone that resides in the endoplasmic reticulum and is required for the normal processing of α 2MR. RAP has the ability to competitively inhibit the binding of all α 2MR to all α 2MR ligands tested. One study shows RAP to bind to complement repeats C5-C7 in cluster II (Cl-II) of α 2MR (Horn *et al.*, 1997, J. Biol. Chem. 272:13608-13613); another shows RAP to bind to all two 20 complement repeat-modules in Cl-II except the C9-C10 module (Andersen *et al.*, J. Biol. Chem., Mar. 24, 2000, PMID: 10747921; published electronically ahead of print). Three structural domains, 1, 2 and 3, have been identified in RAP, consisting of amino acid residues 18-112, 113-218 and 219-323, respectively. Ligand competition titration of recombinant RAP domains indicates that determinants for the inhibition of test ligands 25 reside in the C-terminal regions of domains 1 and 3 (Ellgaard *et al.*, 1997, Eur. J. Biochem. 244:544-51).

2.4. ANTIGEN PRESENTATION

Major histocompatibility complex (MHC) molecules present antigens on the cell 30 surface of antigen-presenting cells. Cytotoxic T lymphocytes (CTLs) then recognize MHC molecules and their associated peptides and kill the target cell. Antigens are processed by two distinct antigen processing routes depending upon whether their origin is intracellular or extracellular. Intracellular or endogenous protein antigens, *i.e.*, antigens synthesized within the antigen-presenting cell, are presented by MHC class I (MHC I) molecules to CD8+ 35 cytotoxic T lymphocytes. On the other hand, extracellular or exogenously synthesized antigenic determinants are presented on the cell surface of "specialized" or "professional"

APCs (macrophages, for example) by MHC class II molecules to CD4+ T cells (see, generally, *Fundamental Immunology*, W.E. Paul (ed.), New York: Raven Press, 1984). This compartmental segregation of antigen processing routes is important to prevent tissue destruction that could otherwise occur during an immune response as a result of shedding of 5 neighboring cell MHC I antigens.

The heat shock protein gp96 chaperones a wide array of peptides, depending upon the source from which gp96 is isolated (for review, see Srivastava *et al.*, 1998, *Immunity* 8: 657-665). Tumor-derived gp96 carries tumor-antigenic peptides (Ishii *et al.*, 1999, *J. Immunology* 162:1303-1309); gp96 preparations from virus-infected cells carry viral 10 epitopes (Suto and Srivastava, 1995, *Science* 269:1585-1588; Nieland *et al.*, 1998, *Proc. Natl. Acad. Sci. USA* 95:1800-1805), and gp96 preparations from cells transfected with model antigens such as ovalbumin or β -galactosidase are associated with the corresponding 15 epitopes (Arnold *et al.*, 1995, *J. Exp. Med.* 182:885-889; Breloer *et al.*, 1998, *Eur. J. Immunol.* 28:1016-1021). The association of gp96 with peptides occurs *in vivo* (Menoret 20 and Srivastava, 1999, *Biochem. Biophys. Research Commun.* 262:813-818). Gp96-peptide complexes, whether isolated from cells (Tamura *et al.*, 1997, *Science* 278:117-120), or reconstituted *in vitro* (Blachere *et al.*, 1997, *J. Exp. Med.* 186:1183-1406) are excellent 15 immunogens and have been used extensively to elicit CD8+ T cell responses specific for the gp96-chaperoned antigenic peptides.

20 The capacity of gp96-peptide complexes to elicit an immune response is dependent upon the transfer of the peptide to MHC class I molecules of antigen-presenting cells (Suto and Srivastava, 1995, *supra*). Endogenously synthesized antigens chaperoned by gp96 in the endoplasmic reticulum [ER] can prime antigen-specific CD8+ T cells (or MHC I-restricted CTLs) *in vivo*; this priming of CD8+ T cells requires macrophages. However, the process 25 whereby exogenously introduced gp96-peptide complexes elicit the antigen-specific CD8+ T cell response is not completely understood since there is no established pathway for the translocation of extracellular antigens into the class I presentation machinery. Yet antigenic peptides of extracellular origin associated with HSPs are somehow salvaged by macrophages, channeled into the endogenous pathway, and presented by MHC I molecules to be recognized 30 by CD8+ lymphocytes (Suto and Srivastava, 1995, *supra*; Blachere *et al.*, 1997, *J. Exp. Med.* 186:1315-22).

35 Several models have been proposed to explain the delivery of extracellular peptides for antigen presentation. One proposal, known as the "direct transfer" model, suggests that HSP-chaperoned peptides are transferred to MHC I molecules on the cell surface of macrophages for presentation to CD8+ T lymphocytes. Another suggestion is that soluble extracellular proteins can be trafficked to the cytosol via constitutive macropinocytosis in

bone marrow-derived macrophages and dendritic cells (Norbury *et al.*, 1997, Eur. J. Immunol. 27:280-288). Yet another proposed mechanism is that HSPs are taken up by the MHC class I molecules of the macrophage, which stimulate the appropriate T cells (Srivastava *et al.*, 1994, Immunogenetics 39:93-98. Others have suggested that a novel 5 intracellular trafficking pathway may be involved for the transport of peptides from the extracellular medium into the lumen of ER (Day *et al.*, 1997, Proc. Natl. Acad. Sci. 94:8064-8069; Nicchitta, 1998, Curr. Opin. in Immunol. 10:103-109). Further suggestions include the involvement of phagocytes which (a) possess an ill-defined pathway to shunt protein from the phagosome into the cytosol where it would enter the normal class I pathway; (b) digest 10 ingested material in lysosomes and regurgitate peptides for loading on the surface to class I molecules (Bevan, 1995, J. Exp. Med. 182:639-41).

Still others have proposed a receptor-mediated pathway for the delivery of extracellular peptides to the cell surface of APCs for antigen presentation. In view of the extremely small quantity of gp96-chaperoned antigenic peptides required for immunization 15 (Blachere *et al.*, 1997, *supra*), and the strict dependence of immunogenicity of gp96-peptide complexes on functional antigen presenting cells (APCs) (Udono *et al.*, 1994, Proc. Natl. Acad. Sci. U.S.A. 91:3077-3081), APCs had been proposed to possess receptors for gp96 (Srivastava *et al.*, 1994, Immunogenetics 39:93-98). Preliminary microscopic evidence consistent with such receptors has been recently obtained (Binder *et al.*, 1998, Cell Stress & 20 Chaperones 3 (Supp.1):2.; Arnold-Schild *et al.*, 1999, J. Immunol. 162: 3757-3760; and Wassenberg *et al.*, 1999, J. Cell Sci. 1:12). One hypothesis is that the mannose receptor is used in the uptake of gp96, but no mechanism has been proposed for the non-glycosylated HSPs, such as Hsp70 (Ciupitu *et al.*, 1998, J. Exp. Med., 187:685-691).

The identification and characterization of specific molecules involved in HSP- 25 mediated antigen presentation of peptides could provide useful reagents and techniques for eliciting specific immunity by HSP and HSP-peptide complexes, and for developing novel diagnostic and therapeutic methods.

Citation or discussion of a reference herein shall not be construed as an admission that such is prior art to the present invention.

30

3. SUMMARY OF THE INVENTION

The present invention relates to compositions and methods for the use of the alpha (2) 35 macroglobulin ("α2M") receptor as a heat shock protein receptor. The invention is based, in part, on the Applicant's discovery that the α2M receptor is a cell surface receptor for heat shock proteins. In particular, the Applicant has shown that the heat shock protein gp96 binds

directly to the α 2M receptor, and that α 2M inhibits re-presentation of gp96-chaperoned antigenic peptides by macrophages. Because no precedent exists for receptors that recognize abundant and intracellular proteins like HSPs, the discovery of an HSP cell surface receptor was highly unexpected.

5 The present invention provides compositions comprising complexes of HSPs and the α 2M receptor, and antibodies and other molecules that bind the HSP- α 2M receptor complex. The invention also encompasses methods for the use of the α 2M receptor as a heat shock protein receptor, including methods for screening for compounds that modulate the interaction of HSP and the α 2M receptor, and methods for treatment and detection of HSP-
10 α 2M receptor-mediated processes and HSP- α 2M receptor-related disorders and conditions, such as autoimmune disorders, proliferative disorders and infectious diseases.

The invention provides a method for identifying a compound that modulates an HSP- α 2M receptor-mediated process, comprising: (a) contacting a test compound with a heat shock protein and an alpha (2) macroglobulin receptor; and (b) measuring the level of alpha
15 (2) macroglobulin receptor activity or expression, such that if the level of activity or expression measured in (b) differs from the level of alpha (2) macroglobulin receptor activity in the absence of the test compound, then a compound that modulates an HSP- α 2M receptor-mediated process is identified. In one embodiment of this method the compound identified is an antagonist which interferes with the interaction of the heat shock protein with
20 the alpha (2) macroglobulin receptor, further comprising the step of: (c) determining whether the level interferes with the interaction of the heat shock protein and the alpha(2) macroglobulin receptor. In another embodiment, the test compound is an antibody specific for the alpha (2) macroglobulin receptor. In another embodiment, the test compound is an antibody specific for alpha (2) macroglobulin. In another embodiment, test compound is an
25 antibody specific for a heat shock protein. In another embodiment, the test compound is a small molecule. In another yet embodiment, the test compound is a peptide. In another embodiment, the peptide comprises at least 5 consecutive amino acids of the alpha (2) macroglobulin receptor. In yet another embodiment, the peptide comprises at least 5 consecutive amino acids of alpha (2) macroglobulin. In yet another embodiment, the peptide
30 comprises at least 5 consecutive amino acids of a heat shock protein sequence. In another embodiment, the compound is an agonist which enhances the interaction of the heat shock protein with the alpha (2) macroglobulin receptor. In another embodiment, which the HSP- α 2M receptor-mediated process affects an autoimmune disorder, a disease or disorder involving disruption of antigen presentation or endocytosis, a disease or disorder involving
35 cytokine clearance or inflammation, a proliferative disorder, a viral disorder or other infectious disease, hypercholesterolemia, Alzheimer's disease, diabetes, or osteoporosis.

The invention also provides a method for identifying a compound that modulates an HSP- α 2M receptor-mediated process, comprising: (a) contacting a test compound with a heat shock protein and an alpha (2) macroglobulin receptor-expressing cell; and (b) measuring the level of alpha (2) macroglobulin receptor activity or expression in the cell, such that if the level of activity or expression measured in (b) differs from the level of alpha (2) macroglobulin receptor activity in the absence of the test compound, then a compound that modulates an HSP- α 2M receptor-mediated process is identified. In yet another embodiment, wherein the alpha (2) macroglobulin receptor activity measured is the ability to interact with a heat shock protein.

The invention also encompasses a method for identifying a compound that modulates the binding of a heat shock protein to the α 2M receptor, comprising: (a) contacting a heat shock protein with an alpha (2) macroglobulin receptor, or fragment, or analog, derivative or mimetic thereof, in the presence of a test compound; and (b) measuring the amount of heat shock protein bound to the alpha (2) macroglobulin receptor, or fragment, analog, derivative or mimetic thereof, such that if the amount of bound heat shock protein measured in (b) differs from the amount of bound heat shock protein measured in the absence of the test compound, then a compound that modulates the binding of an HSP to the α 2M receptor is identified. In another embodiment, alpha (2) macroglobulin receptor contacted in step (a) is on a cell surface. In another embodiment, the alpha (2) macroglobulin receptor is immobilized to a solid surface. In another embodiment, the solid surface is a microtiter dish. In another embodiment, the amount of bound heat shock protein is measured by contacting the cell with a heat shock protein-specific antibody. In yet another embodiment, the heat shock protein is labeled and the amount of bound heat shock protein is measured by detecting the label. In another embodiment, the heat shock protein is labeled with a fluorescent label.

The invention further provides a method for identifying a compound that modulates heat shock protein-mediated antigen presentation by alpha (2) macroglobulin receptor-expressing cells comprising: (a) adding a test compound to a mixture of alpha (2) macroglobulin receptor-expressing cells and a complex consisting essentially of a heat shock protein noncovalently associated with an antigenic molecule, under conditions conducive to alpha (2) macroglobulin receptor-mediated endocytosis; (b) measuring the level of antigen-specific stimulation of cytotoxic T cells by alpha (2) macroglobulin receptor-expressing cells, such that if the level measured in (b) differs from the level of said stimulation in the absence of the test compound, then a compound that modulates heat shock protein-mediated antigen presentation by alpha (2) macroglobulin receptor-expressing cells is identified. In one embodiment of this method, the step of measuring the level of the antigenic molecule presented on the cell surface of step (b) comprises: (i) adding the alpha (2) macroglobulin

receptor-expressing cells formed in step (a) to T cells under conditions conducive to the activation of the T cells; and (ii) comparing the level of activation of said cytotoxic T cells with the level of activation of T cells by an alpha (2) macroglobulin receptor-expressing cell formed in the absence of the test compound, wherein an increase or decrease in level of T 5 cell activation indicates that a compound that modulates heat shock protein-mediated antigen presentation by alpha (2) macroglobulin receptor-expressing cells is identified.

In various embodiments, the heat shock protein used in the methods of the invention is gp96.

In another embodiment, the invention provides a method for detecting a heat shock 10 protein-alpha (2) macroglobulin receptor-related disorder in a mammal comprising measuring the level of an HSP-alpha (2) macroglobulin receptor-mediated process in a patient sample, such that if the measured level differs from the level found in clinically normal individuals, then a heat shock protein-alpha (2) macroglobulin receptor-related disorder is detected.

15 The invention also encompasses kits comprising compositions of the invention. In one embodiment, a kit is provided, packaged in one or more containers, comprising: (a) a purified heat shock protein, nucleic acid encoding a heat shock protein, or cell expressing a heat shock protein; and (b) an alpha (2) macroglobulin receptor polypeptide, nucleic acid encoding an alpha (2) macroglobulin receptor polypeptide, or cell expressing an alpha (2) 20 macroglobulin receptor polypeptide. In one embodiment, the kit the alpha (2) macroglobulin receptor polypeptide, nucleic acid encoding an alpha (2) macroglobulin receptor polypeptide, or cell expressing an alpha (2) macroglobulin receptor polypeptide is purified. In another embodiment, the kit further comprises instructions for use in treating an autoimmune disorder, an infectious disease, or a proliferative disorder.

25 The invention also provides a method for modulating an immune response comprising administering to a mammal a purified compound that modulates the interaction of a heat shock protein with the alpha (2) macroglobulin receptor. In one embodiment, the compound is an agonist which enhances the interaction of the heat shock protein and the alpha (2) macroglobulin receptor. In another embodiment of this method the compound in an 30 antagonist that interferes with the interaction between the heat shock protein and the α 2M receptor.

The invention further provides a method for treating an autoimmune disorder comprising administering to a mammal in need of such treatment a purified compound that interferes with the interaction of a heat shock protein with the alpha (2) macroglobulin 35 receptor. In one embodiment of this method the compound in an antagonist that interferes with the interaction between the heat shock protein and the α 2M receptor. In one

embodiment, the antagonist is an antibody specific for alpha (2) macroglobulin receptor. In another embodiment, the antagonist is an antibody specific for a heat shock protein. In another embodiment, the antagonist is a small molecule. In another embodiment, the antagonist is a peptide. In another embodiment, the peptide comprises at least 5 consecutive 5 amino acids of alpha (2) macroglobulin receptor. In another embodiment, the peptide comprises at least 5 consecutive amino acids of alpha (2) macroglobulin. In another embodiment, the peptide comprises at least 5 consecutive amino acids of a heat shock protein sequence.

The invention further provides a method for increasing the immunopotency of a 10 cancer cell or an infected cell comprising transforming said cell with a nucleic acid comprising a nucleotide sequence that (i) is operably linked to a promoter, and (ii) encodes an alpha (2) macroglobulin receptor polypeptide.

Still further, the invention provides a method for increasing the immunopotency of a cancer cell or an infected cell comprising: (a) transforming said cell with a nucleic acid 15 comprising a nucleotide sequence that (i) is operably linked to a promoter, and (ii) encodes an alpha (2) macroglobulin receptor polypeptide, and (b) administering said cell to an individual in need of treatment, so as to obtain an elevated immune response.

The invention also provides a recombinant cancer cell transformed with a nucleic acid comprising a nucleotide sequence that (i) is operably linked to a promoter, and (ii) encodes 20 an alpha (2) macroglobulin receptor polypeptide. In one embodiment, the recombinant cell is a human cell.

In yet another embodiment, the invention provides a recombinant infected cell transformed with a nucleic acid comprising a nucleotide sequence that (i) is operably linked to a promoter, and (ii) encodes an alpha (2) macroglobulin receptor polypeptide. In one 25 embodiment, the recombinant cell is a human cell.

The term "HSP- α 2M receptor-mediated process" as used herein refers to a process dependent and/or responsive, either directly or indirectly, to the interaction of HSP with the α 2M receptor. Such processes include processes that result from an aberrant level of expression, synthesis and/or activity of α 2M receptor, such as endocytic activities relating to 30 the binding of the various α 2M ligands, including but not limited to HSP, α 2M, lipoprotein complexes, lactoferrin, tissue-type plasminogen activator (tPA), urokinase-type plasminogen activator (uPA), and exotoxins. Such processes include, but are not limited to, endocytosis, antigen presentation, cholesterol regulation, apoE-containing lipoprotein clearance, and chylomicron remnant removal.

35 The terms "HSP- α 2M receptor-related disorder" and "HSP- α 2M receptor-related condition", as used herein, refers to a disorder and a condition, respectively, involving a

HSP- α 2M receptor interaction. Such disorders and conditions may result, for example, from an aberrant ability of the α 2M receptor to interact with HSP, perhaps due to aberrant levels of HSP and/or α 2M receptor expression, synthesis and/or activity relative to levels found in normal, unaffected, unimpaired individuals, levels found in clinically normal individuals, and/or levels found in a population whose levels represent a baseline, average HSP and/or α 2M receptor levels. Such disorders include, but are not limited to, autoimmune disorders, diseases and disorders involving disruption of antigen presentation and/or endocytosis, diseases and disorders involving cytokine clearance and/or inflammation, proliferative disorders, viral disorders and other infectious diseases, hypercholesterolemia, Alzheimer's disease, diabetes, and osteoporosis.

4. BRIEF DESCRIPTION OF THE FIGURES

FIG. 1A-C. Identification of an 80 kDa polypeptide as a putative gp96 receptor. **A.** Confocal microscopy of re-presentation-competent RAW264.7 cells stained with gp96-FITC (left panel) and with albumin-FITC (right panel). **B.** SDS-PAGE analysis of detergent extracts of plasma membranes from surface biotinylated RAW264.7 (re-presentation-competent) or P815 cells (representation-incompetent) eluted from gp96 or albumin-Sepharose (SA) columns and stained with silver stain (top) or avidin-peroxidase (bottom). **C.** gp96-SASD-I¹²⁵ was cross-linked to live peritoneal macrophages (MO) or P815 cells, and the cell lysates examined by SDS-PAGE and autoradiography. Various components were omitted as controls, as indicated.

FIG. 2A-B. Anti-p80 antiserum detects an 80 kDa molecule and inhibits re-presentation of gp96-chaperoned AH1 peptide by macrophage. **A.** Pre-immune and immune sera were used to probe blots of plasma membrane extracts of RAW264.7, peritoneal macrophages (both cell types re-presentation-competent), or P815 cells. **B.** Re-presentation of gp96-chaperoned peptide AH1. Sera were added at the final dilution indicated. The solid cross indicates the level of T cell stimulation when the APCs were pulsed directly with the AH1 peptide. The open cross indicates the corresponding value with unpulsed APCs.

FIG. 3A-C. Protein microsequencing of the 80 kDa protein. **A.** Analysis of a single tryptic (GALHIYHQR) peptide by tandem- mass spectrometry. All possible b- and y-ion series together with identified b-ion series (red) and y-ion series (blue) are shown. **B.** Collision-

induced dissociation (CID) spectrum of this peptide is shown. **C.** Four identified peptides from the α 2M receptor, peptide mass, and sequence are shown.

FIG. 4. α 2-Macroglobulin inhibits re-presentation of gp96-chaperoned AH1 peptide by 5 macrophage. The solid cross indicates the level of T cell stimulation when the APCs were pulsed directly with the AH1 peptide. The open cross indicates the corresponding value with unpulsed APCs.

FIG. 5. α 2M receptor is a sensor of necrotic cell death due to its ability to detect 10 extracellular gp96. Conversely, receptors (psR) for phosphatidyl serine (ps) detect apoptotic cell death.

FIG. 6A. The mouse α 2MR cDNA (SEQ ID NO:1) and predicted open reading frame of 15 murine α 2MR protein (Genbank accession no. CAA47817). **B.** The murine α 2M protein (SEQ ID NO:2), with residues identified by microsequencing an 80 kDa, gp96-interacting fragment of the receptor highlighted in bold.

FIG. 7A. The human α 2M cDNA (SEQ ID NO:3) and predicted open reading frame of α 2M 20 protein (SEQ ID NO:4)(Genbank accession no. M11313). **B.** The sequence of the mature human α 2M protein (SEQ ID NO:5), following cleavage of the N-terminal 23 amino acid signal sequence. Highlighted residues represent the 138 amino acid α 2MR-binding domain (RBD). Underlined residues represent an extension of the RBD that is present in a α 2MR-binding, proteolytic fragment of α 2M (RBDv). Bolded residues have been shown to be 25 important for α 2MR binding. Italicized residues represent a domain that is conserved among ligands of α 2MR.

FIG. 8A. The human α 2MR cDNA (SEQ ID NO:6) and predicted open reading frame of 30 human α 2MR protein (Genbank accession no. NP_002323). **B.** Primary amino acid sequence of human α 2MR (SEQ ID NO:7). The approximate locations of complement repeat clusters I and II are highlighted in grey. Individual complement repeats of Cl-II are indicated as follows: amino acids of CR3, 5, 7 and 9 are in italics, and amino acids of CR4, 6, 8, and 10 are underlined. Amino acids highlighted in bold were present in an 80kDa peptide fragment of the mouse α 2MR that bound to gp96. The double underlined residues represent the 35 predicted signal peptide. For the locations of other features of the receptor, such as the EGF repeats, see the article by (Herz *et al.*, 1988, EMBO J. 7:4119-4127).

5. DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compositions and methods for the use of the alpha (2) macroglobulin ("α2M") receptor as a heat shock protein receptor. In particular, the present invention provides compositions comprising isolated HSP-α2M receptor complexes, including isolated and/or recombinant cells, and antibodies, molecules and compounds that modulate the interaction of an HSP with the α2M receptor. The invention further encompasses methods for the use of the α2M receptor as a heat shock protein receptor, including screening assays to identify compounds that modulate the interaction of an HSP with the α2M receptor, and methods for the use of these molecules and complexes for the diagnosis and treatment of immune disorders, proliferative disorders, and infectious diseases.

A heat shock protein, or "HSP", useful in the practice of the invention may be selected from among any cellular protein that satisfies any one of the following criteria: the intracellular concentration of an HSP increases when a cell is exposed to a stressful stimulus; an HSP can bind other proteins or peptides, and can release the bound proteins or peptides in the presence of adenosine triphosphate (ATP) or low pH; or an HSP possesses at least 35% homology with any cellular protein having any of the above properties. Preferably, the HSP used in the compositions and methods of the present invention includes, but are not limited to, HSP90, gp96, BiP, Hsp70, DnaK, Hsc70, PhoE calreticulin, PDI, or an sHsp, alone or in combination.

20 In a preferred embodiment, an HSP is a mammalian (e.g., mouse, rat, primate, domestic animal such as dog, cat, cow, horse), and is most preferably, human.

25 Hsps useful in the practice of the invention include, but are not limited to, members of the HSP60 family, HSP70 family, HSP90 family, HSP100 family, sHSP family, calreticulin, PDI, and other proteins in the endoplasmic reticulum that contain thioredoxin-like domain(s), such as, but not limited to, ERp72 and ERp61.

30 HSP analogs, muteins, derivatives, and fragments can also be used in place of HSPs according to the invention. An HSP peptide-binding "fragment" for use in the invention refers to a polypeptide comprising a HSP peptide-binding domain that is capable of becoming non-covalently associated with a peptide to form a complex that is capable of eliciting an immune response. In one embodiment, an HSP peptide-binding fragment is a polypeptide comprising an HSP peptide-binding domain of approximately 100 to 200 amino acids.

35 Databases can also be searched to identify sequences with various degrees of similarities to a query sequence using programs, such as FASTA and BLAST, which rank the similar sequences by alignment scores and statistics. Such nucleotide sequences of non-

limiting examples of HSPs that can be used for preparation of the HSPs used in the methods of the invention are as follows: human Hsp70, Genbank Accession No. NM_005345, Sargent *et al.*, 1989, Proc. Natl. Acad. Sci. U.S.A., 86:1968-1972; human Hsp90, Genbank Accession No. X15183, Yamazaki *et al.*, Nucl. Acids Res. 17:7108; human gp96: Genbank Accession No. X15187, Maki *et al.*, 1990, Proc. Natl. Acad Sci., 87: 5658-5562; human BiP: Genbank Accession No. M19645; Ting *et al.*, 1988, DNA 7: 275-286; human Hsp27, Genbank Accession No. M24743; Hickey *et al.*, 1986, Nucleic Acids Res. 14:4127-45; mouse Hsp70: Genbank Accession No. M35021, Hunt *et al.*, 1990, Gene, 87:199-204; mouse gp96: Genbank Accession No. M16370, Srivastava *et al.*, 1987, Proc. Natl. Acad. Sci., 85:3807-3811; and mouse BiP: Genbank Accession No. U16277, Haas *et al.*, 1988, Proc. Natl. Acad. Sci. U.S.A., 85: 2250-2254. Due to the degeneracy of the genetic code, the term "HSP sequence", as used herein, refers not only to the naturally occurring amino acid and nucleotide sequence but also encompasses all the other degenerate sequences that encode the HSP.

The aforementioned HSP families also contain proteins that are related to HSPs in sequence, for example, having greater than 35% amino acid identity, but whose expression levels are not altered by stress. Therefore, it is contemplated that the definition of heat shock or stress protein, as used herein, embraces other proteins, mutants, analogs, and variants thereof having at least 35% to 55%, preferably 55% to 75%, and most preferably 75% to 85% amino acid identity with members of these families whose expression levels in a cell are enhanced in response to a stressful stimulus. The determination of percent identity between two sequences can also be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul, 1990, Proc. Natl. Acad. Sci. USA 87:2264-2268, modified as in Karlin and Altschul, 1993, Proc. Natl. Acad. Sci. USA 90:5873-5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul, *et al.*, 1990, J. Mol. Biol. 215:403-410. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, 1997, Nucleic Acids Res.25:3389-3402. Alternatively, PSI-Blast can be used to perform an iterated search which detects distant relationships between molecules (Altschul *et al.*, 1997, *supra*). When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used

(see <http://www.ncbi.nlm.nih.gov>). Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, 1988, CABIOS 4:11-17. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package.

5 When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used.

The immunogenic HSP-peptide complexes of the invention may include any complex containing an HSP and a peptide that is capable of inducing an immune response in a mammal. The peptides are preferably noncovalently associated with the HSP. Preferred 10 complexes may include, but are not limited to, gp96-peptide complexes, HSP90-peptide complexes, HSP70-peptide complexes, HSP60-peptide complexes, HSP100-peptide complexes, calreticulin-peptide complexes, and sHSP-peptide complexes. For example, the HSP gp96 which is present in the endoplasmic reticulum of eukaryotic cells and is related to the cytoplasmic HSP90's can be used to generate an effective vaccine containing a gp96-peptide complex. 15

The HSPs, α 2M receptor, and/or antigenic molecules for use in the invention can be purified from natural sources, chemically synthesized, or recombinantly produced. Although the HSPs may be allogeneic to the patient, in a preferred embodiment, the HSPs are autologous to the patient to whom they are administered.

20

5.1 COMPOSITIONS OF THE INVENTION

The present invention provides compositions that increase or decrease the interaction between an HSP and the α 2M receptor which can be used to elicit an immune response. Such compositions also include antibodies that specifically recognize HSP- α 2M receptor 25 complexes, isolated cells that express HSP- α 2M receptor complexes, and isolated and recombinant cells that contain recombinant α 2M receptor and HSP sequences. In addition, in various methods of the invention, sequences encoding the α 2M receptor, an HSP, and α 2M are used for immunotherapy. Such compositions can be used, for example, in immunotherapy against proliferative disorders, infectious diseases, and other HSP- α 2M 30 receptor-related disorders. Methods for the synthesis and production of such compositions are described herein.

5.1.1 RECOMBINANT EXPRESSION

In various embodiments of the invention, sequences encoding the α 2M receptor, an HSP, or α 2M are inserted into an expression vector for propagation and expression in recombinant cells. Thus, in one embodiment, the α 2M receptor, HSP, or α 2M coding region 5 is linked to a non-native promoter for expression in recombinant cells.

The amino acid sequence of the portion of the α 2M receptor that recognizes and binds to HSPs is shown in FIG. 6B (SEQ ID NO:2). Based on the discovery by the Applicant, this portion of the α 2M receptor is responsible for recognizing and binding to HSPs and HSP-antigenic peptide complexes. After binding HSPs, the α 2M receptor facilitates transport of 10 the HSP-antigenic peptide complex into the cell, where the peptide antigens associate with MHC class I molecules and are then presented on the cell surface of the cell, and become available to stimulate an immune response. Based on this invention, compositions comprising agonists and antagonists of the α 2M receptor and HSPs interactions can be used to modulate the immune response. Thus, recombinant α 2M receptor polypeptides, 15 complexes of α 2M receptor and an HSP or HSP-antigenic peptide complexes, and recombinant cells expressing the α 2M receptor or the α 2M receptor and antigenic peptides can be used in methods for immunotherapy and diagnostic methods described herein.

In various embodiments of the invention, sequences encoding the α 2M receptor, and/or a heat shock protein or α 2M, or fragments thereof, are inserted into an expression 20 vector for propagation and expression in recombinant cells. An expression construct, as used herein, refers to a nucleotide sequence encoding a particular gene product, such as the α 2M receptor, HSP or α 2M, operably associated with one or more regulatory regions which allows expression of the encoded gene product in an appropriate host cell. "Operably-associated" refers to an association in which the regulatory regions and the nucleotide 25 sequence encoding the gene product to be expressed are joined and positioned in such a way as to permit transcription, and ultimately, translation.

The DNA may be obtained from known sequences derived from sequence databases by standard procedures known in the art by DNA amplification or molecular cloning directly from a tissue, cell culture, or cloned DNA (e.g., a DNA "library"). Any eukaryotic cell may 30 serve as the nucleic acid source for obtaining the coding region of an hsp gene. Nucleic acid sequences encoding HSPs can be isolated from vertebrate, mammalian, as well as primate sources, including humans. Clones derived from genomic DNA may contain regulatory and intron DNA regions in addition to coding regions; clones derived from cDNA will contain only exon sequences. Whatever the source, the hsp gene should be cloned into a suitable 35 vector for propagation of the gene.

Vectors based on *E. coli* are the most popular and versatile systems for high level expression of foreign proteins (Makrides, 1996, *Microbiol Rev*, 60:512-538). Non-limiting examples of regulatory regions that can be used for expression in *E. coli* may include but not limited to *lac*, *trp*, *lpp*, *phoA*, *recA*, *tac*, λP_L , and phage T3 and T7 promoters (Makrides, 1996, *Microbiol Rev*, 60:512-538). Non-limiting examples of prokaryotic expression vectors may include the λ gt vector series such as λ gt11 (Huynh et al., 1984 in "DNA Cloning Techniques", Vol. I: A Practical Approach (D. Glover, ed.), pp. 49-78, IRL Press, Oxford), and the pET vector series (Studier et al., 1990, *Methods Enzymol.*, 185:60-89). However, a potential drawback of a prokaryotic host-vector system is the inability to perform many of the post-translational processing events of mammalian cells. Thus, an eukaryotic host-vector system is preferred, a mammalian host-vector system is more preferred, and a human host-vector system is the most preferred.

The regulatory regions necessary for transcription of the α 2M receptor sequence, for example, can be provided by the expression vector. A translation initiation codon (ATG) may also be provided to express a nucleotide sequence encoding an α 2M receptor that lacks an initiation codon. In a compatible host-construct system, cellular proteins required for transcription, such as RNA polymerase and transcription factors, will bind to the regulatory regions on the expression construct to effect transcription of the α 2M receptor sequence in the host organism. The precise nature of the regulatory regions needed for gene expression may vary from host cell to host cell. Generally, a promoter is required which is capable of binding RNA polymerase to initiate the transcription of an operably-associated nucleic acid sequence. Such regulatory regions may include those 5'-non-coding sequences involved with initiation of transcription and translation, such as the TATA box, the cap site, a CAAT box, and the like. The non-coding region 3' to the coding sequence may contain transcriptional termination regulatory sequences, such as terminators and polyadenylation sites.

Both constitutive and inducible regulatory regions may be used for expression of the α 2M receptor, HSP, or α 2M. It may be desirable to use inducible promoters when the conditions optimal for growth of the recombinant cells and the conditions for high level expression of the gene product are different. Examples of useful regulatory regions are provided in the next section below.

For expression of the α 2M receptor, HSP, or α 2M gene product in mammalian host cells, a variety of regulatory regions can be used, for example, the SV40 early and late promoters, the cytomegalovirus (CMV) immediate early promoter, and the Rous sarcoma virus long terminal repeat (RSV-LTR) promoter. Inducible promoters that may be useful in mammalian cells include but are not limited to those associated with the metallothionein II gene, mouse mammary tumor virus glucocorticoid responsive long terminal repeats (MMTV-

LTR), the β -interferon gene, and the Hsp70 gene (Williams *et al.*, 1989, *Cancer Res.* 49:2735-42; Taylor *et al.*, 1990, *Mol. Cell Biol.*, 10:165-75). It may be advantageous to use heat shock promoters or stress promoters to drive expression of the α 2M receptor in recombinant host cells.

5 The following animal regulatory regions, which exhibit tissue specificity and have been utilized in transgenic animals, can also be used in tumor cells of a particular tissue type: elastase I gene control region which is active in pancreatic acinar cells (Swift *et al.*, 1984, *Cell* 38:639-646; Ornitz *et al.*, 1986, *Cold Spring Harbor Symp. Quant. Biol.* 50:399-409; MacDonald, 1987, *Hepatology* 7:425-515); insulin gene control region which is active in 10 pancreatic beta cells (Hanahan, 1985, *Nature* 315:115-122), immunoglobulin gene control region which is active in lymphoid cells (Grosschedl *et al.*, 1984, *Cell* 38:647-658; Adames *et al.*, 1985, *Nature* 318:533-538; Alexander *et al.*, 1987, *Mol. Cell. Biol.* 7:1436-1444), mouse mammary tumor virus control region which is active in testicular, breast, lymphoid and mast cells (Leder *et al.*, 1986, *Cell* 45:485-495), albumin gene control region which is 15 active in liver (Pinkert *et al.*, 1987, *Genes and Devel.* 1:268-276), alpha-fetoprotein gene control region which is active in liver (Krumlauf *et al.*, 1985, *Mol. Cell. Biol.* 5:1639-1648; Hammer *et al.*, 1987, *Science* 235:53-58; alpha 1-antitrypsin gene control region which is active in the liver (Kelsey *et al.*, 1987, *Genes and Devel.* 1:161-171), beta-globin gene control region which is active in myeloid cells (Mogram *et al.*, 1985, *Nature* 315:338-340; 20 Kollias *et al.*, 1986, *Cell* 46:89-94; myelin basic protein gene control region which is active in oligodendrocyte cells in the brain (Readhead *et al.*, 1987, *Cell* 48:703-712); myosin light chain-2 gene control region which is active in skeletal muscle (Sani, 1985, *Nature* 314:283-286), and gonadotropin releasing hormone gene control region which is active in the hypothalamus (Mason *et al.*, 1986, *Science* 234:1372-1378).

25 The efficiency of expression of the α 2M receptor in a host cell may be enhanced by the inclusion of appropriate transcription enhancer elements in the expression vector, such as those found in SV40 virus, Hepatitis B virus, cytomegalovirus, immunoglobulin genes, metallothionein, β -actin (see Bittner *et al.*, 1987, *Methods in Enzymol.* 153:516-544; Gorman, 1990, *Curr. Op. in Biotechnol.* 1:36-47).

30 The expression vector may also contain sequences that permit maintenance and replication of the vector in more than one type of host cell, or integration of the vector into the host chromosome. Such sequences may include but are not limited to replication origins, autonomously replicating sequences (ARS), centromere DNA, and telomere DNA. It may also be advantageous to use shuttle vectors that can be replicated and maintained in at least 35 two types of host cells.

In addition, the expression vector may contain selectable or screenable marker genes for initially isolating or identifying host cells that contain DNA encoding an α 2M receptor. For long term, high yield production of α 2M receptor, stable expression in mammalian cells is preferred. A number of selection systems may be used for mammalian cells, including, but 5 not limited, to the Herpes simplex virus thymidine kinase (Wigler et al., 1977, Cell 11:223), hypoxanthine-guanine phosphoribosyltransferase (Szybalski and Szybalski, 1962, Proc. Natl. Acad. Sci. USA 48:2026), and adenine phosphoribosyltransferase (Lowy et al., 1980, Cell 22:817) genes can be employed in *tk*, *hgprt* or *aprt* cells, respectively. Also, antimetabolite 10 resistance can be used as the basis of selection for dihydrofolate reductase (*dhfr*), which confers resistance to methotrexate (Wigler et al., 1980, Natl. Acad. Sci. USA 77:3567; O'Hare et al., 1981, Proc. Natl. Acad. Sci. USA 78:1527); *gpt*, which confers resistance to mycophenolic acid (Mulligan & Berg, 1981, Proc. Natl. Acad. Sci. USA 78:2072); neomycin 15 phosphotransferase (*neo*), which confers resistance to the aminoglycoside G-418 (Colberre-Garapin et al., 1981, J. Mol. Biol. 150:1); and hygromycin phosphotransferase (*hgy*), which confers resistance to hygromycin (Santerre et al., 1984, Gene 30:147). Other selectable 15 markers, such as but not limited to histidinol and ZeocinTM can also be used.

In order to insert the α 2M receptor, HSP, or α 2M DNA sequence into the cloning site of a vector, DNA sequences with regulatory functions, such as promoters, must be attached to DNA sequences encoding the α 2M receptor, HSP, or α 2M, respectively. To do this, 20 linkers or adapters providing the appropriate compatible restriction sites may be ligated to the ends of cDNA or synthetic DNA encoding an α 2M receptor, by techniques well known in the art (Wu et al., 1987, Methods in Enzymol 152:343-349). Cleavage with a restriction enzyme can be followed by modification to create blunt ends by digesting back or filling in single-stranded DNA termini before ligation. Alternatively, a desired restriction enzyme site can be 25 introduced into a fragment of DNA by amplification of the DNA by use of PCR with primers containing the desired restriction enzyme site.

In one embodiment, an expression construct comprising an α 2M receptor sequence operably associated with regulatory regions can be directly introduced into appropriate host cells for expression and production of α 2M receptor without further cloning (see, for 30 example, U.S. Patent No. 5,580,859). The expression constructs may also contain DNA sequences that facilitate integration of the α 2M receptor sequence into the genome of the host cell, e.g., via homologous recombination. In this instance, it is not necessary to employ an expression vector comprising a replication origin suitable for appropriate host cells in order to propagate and express the α 2M receptor in the host cells.

35 Expression constructs containing cloned nucleotide sequence encoding the α 2M receptor, an HSP, or α 2M can be introduced into the host cell by a variety of techniques

known in the art, including but not limited to, for prokaryotic cells, bacterial transformation (Hanahan, 1985, in DNA Cloning, A Practical Approach, 1:109-136), and for eukaryotic cells, calcium phosphate mediated transfection (Wigler et al., 1977, Cell 11:223-232), liposome-mediated transfection (Schaefer-Ridder et al., 1982, Science 215:166-168),
5 electroporation (Wolff et al., 1987, Proc Natl Acad Sci 84:3344), and microinjection (Cappelli, 1980, Cell 22:479-488).

For long term, high yield production of properly processed α 2M receptor, HSP, or α 2M, stable expression in mammalian cells is preferred. Cell lines that stably express the α 2M receptor, HSP, α 2M, or α 2M receptor-peptide complexes may be engineered by using a
10 vector that contains a selectable marker. By way of example but not limitation, following the introduction of the expression constructs, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the expression construct confers resistance to the selection and optimally allows cells to stably integrate the expression construct into their chromosomes and to grow in culture and
15 to be expanded into cell lines. Such cells can be cultured for a long period of time while the desired gene product is expressed continuously.

The recombinant cells may be cultured under standard conditions of temperature, incubation time, optical density, and media composition. Alternatively, recombinant antigenic cells may be cultured under conditions emulating the nutritional and physiological
20 requirements of the cancer cell or infected cell. However, conditions for growth of recombinant cells may be different from those for expression of the α 2M receptor, HSPs, α 2M, or antigenic proteins.

5.1.2 PEPTIDE SYNTHESIS

25 An alternative to producing HSP, α 2M receptor, or α 2M peptides and polypeptides by recombinant techniques is peptide synthesis. For example, a peptide corresponding to a portion of an HSP or an α 2M peptide comprising the receptor-binding domain, which can be used as an antagonist in the therapeutic methods described herein, can be synthesized by use of a peptide synthesizer. Synthetic peptides corresponding to α 2M receptor sequences useful
30 for therapeutic methods described herein can also be produced synthetically. Conventional peptide synthesis may be used or other synthetic protocols well known in the art.

For example, peptides having the amino acid sequence of the α 2M receptor, an HSP or α 2M, or an analog, mutoin, fragment, or derivative thereof, may be synthesized by solid-phase peptide synthesis using procedures similar to those described by Merrifield, 1963, J.
35 Am. Chem. Soc., 85:2149. During synthesis, N- α -protected amino acids having protected

side chains are added stepwise to a growing polypeptide chain linked by its C-terminal and to an insoluble polymeric support i.e., polystyrene beads. The peptides are synthesized by linking an amino group of an N- α -deprotected amino acid to an α -carboxyl group of an N- α -protected amino acid that has been activated by reacting it with a reagent such as

5 dicyclohexylcarbodiimide. The attachment of a free amino group to the activated carboxyl leads to peptide bond formation. The most commonly used N- α -protecting groups include Boc which is acid labile and Fmoc which is base labile. Details of appropriate chemistries, resins, protecting groups, protected amino acids and reagents are well known in the art and so are not discussed in detail herein (See, Atherton, *et al.*, 1989, *Solid Phase Peptide Synthesis: 10 A Practical Approach*, IRL Press, and Bodanszky, 1993, *Peptide Chemistry, A Practical Textbook*, 2nd Ed., Springer-Verlag).

Purification of the resulting α 2M receptor, HSP, or α 2M peptides is accomplished using conventional procedures, such as preparative HPLC using gel permeation, partition and/or ion exchange chromatography. The choice of appropriate matrices and buffers are

15 well known in the art and so are not described in detail herein.

In addition, analogs and derivatives of α 2M receptor, HSP, or α 2M protein can be chemically synthesized. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the α 2M receptor, HSP, or α 2M sequence. Non-classical amino acids include but are not limited to the D- 20 isomers of the common amino acids, α -amino isobutyric acid, 4-amino butyric acid, Abu, 2-amino butyric acid, γ -Abu, ϵ -Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, 25 citrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, β -alanine, fluoro-amino acids, designer amino acids such as β -methyl amino acids, C α -methyl amino acids, N α -methyl amino acids, and amino acid analogs in general.

5.1.3 ANTIBODIES SPECIFIC FOR α 2M RECEPTOR-HSP COMPLEXES

Described herein are methods for the production of antibodies capable of specifically recognizing α 2M receptor epitopes, HSP- α 2M receptor complex epitopes or epitopes of 30 conserved variants or peptide fragments of the receptor or receptor complexes. Such antibodies are useful for therapeutic and diagnostic methods of the invention.

Such antibodies may include, but are not limited to, polyclonal antibodies, monoclonal antibodies (mAbs), humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab')₂ fragments, fragments produced by a Fab expression library, anti- 35 idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above. Such

antibodies may be used, for example, in the detection of an α 2M receptor or HSP- α 2M receptor complex in an biological sample. Such antibodies may also be utilized in conjunction with, for example, compound screening schemes, as described below, in Section 5.2, for the evaluation of the effect of test compounds on the interaction between HSPs and 5 the α 2M receptor.

Anti- α 2M receptor complex antibodies may additionally be used as a method for the inhibition of abnormal receptor product activity. Thus, such antibodies may, be utilized as part of treatment methods for HSP- α 2M receptor related disorders, *e.g.*, autoimmune disorders.

10 For the production of antibodies against α 2M receptor or receptor complexes, various host animals may be immunized by injection with an α 2M receptor or HSP- α 2M receptor complex, or a portion thereof. An antigenic portion of α 2M receptor or HSP- α 2M receptor complex can be readily predicted by algorithms known in the art.

15 Host animals may include, but are not limited to rabbits, mice, and rats, to name but a few. Various adjuvants may be used to increase the immunological response, depending on the host species, including but not limited to Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanin, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and

20 *Corynebacterium parvum*.

25 Polyclonal antibodies are heterogeneous populations of antibody molecules derived from the sera of animals immunized with an antigen, such as an α 2M receptor or HSP- α 2M receptor complex, or an antigenic functional derivative thereof. For the production of polyclonal antibodies, host animals such as those described above, may be immunized by injection with α 2M receptor or HSP- α 2M receptor complex, or portion thereof, supplemented with adjuvants as also described above.

30 Monoclonal antibodies, which are homogeneous populations of antibodies to a particular antigen, may be obtained by any technique that provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique of Kohler and Milstein, (1975, *Nature* 256, 495-497; and U.S. Patent No. 4,376,110), the human B-cell hybridoma technique (Kosbor *et al.*, 1983, *Immunology Today* 4: 72; Cole *et al.*, 1983, *Proc. Natl. Acad. Sci. USA* 80, 2026-2030), and the EBV-hybridoma technique (Cole *et al.*, 1985, *Monoclonal Antibodies And Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96). Such antibodies may be of any immunoglobulin 35 class including IgG, IgM, IgE, IgA, IgD and any subclass thereof. The hybridoma producing

the mAb of this invention may be cultivated *in vitro* or *in vivo*. Production of high titers of mAbs *in vivo* makes this the presently preferred method of production.

In addition, techniques developed for the production of "chimeric antibodies" (Morrison, *et al.*, 1984, Proc. Natl. Acad. Sci., 81: 6851-6855; Neuberger, *et al.*, 1984, 5 Nature 312: 604-608; Takeda, *et al.*, 1985, Nature, 314: 452-454) by splicing the genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human 10 immunoglobulin constant region (see, *e.g.*, Cabilly *et al.*, U.S. Patent No. 4,816,567; and Boss *et al.*, U.S. Patent No. 4,816397, which are incorporated herein by reference in their entirety).

In an additional embodiment of the invention, monoclonal antibodies can be produced in germ-free animals (see PCT International Publication No. WO 89/12690, published 15 December 12, 1989). According to the invention, human antibodies may be used and can be obtained by using human hybridomas (Cote *et al.*, 1983, Proc. Natl. Acad. Sci. U.S.A. 80:2026-2030) or by transforming human B cells with EBV virus *in vitro* (Cole *et al.*, 1985, in Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, pp. 77-96). Techniques developed for the production of "chimeric antibodies" (Morrison *et al.*, 1984, Proc. Natl. 20 Acad. Sci. U.S.A. 81:6851-6855; Neuberger *et al.*, 1984, Nature 312:604-608; Takeda *et al.*, 1985, Nature 314:452-454) by splicing the genes from a mouse antibody molecule specific for an α 2M receptor-HSP complex together with genes from a human antibody molecule of appropriate biological activity can also be used; such antibodies are within the scope of this invention.

25 Humanized antibodies are also provided (see U.S. Patent No. 5,225,539 by Winter). An immunoglobulin light or heavy chain variable region consists of a "framework" region interrupted by three hypervariable regions, referred to as complementarity determining regions (CDRs). The extent of the framework region and CDRs have been precisely defined (see, "Sequences of Proteins of Immunological Interest", Kabat, E. *et al.*, U.S. Department of 30 Health and Human Services (1983). Briefly, humanized antibodies are antibody molecules from non-human species having one or more CDRs from the non-human species and a framework region from a human immunoglobulin molecule. Such CDRS-grafted antibodies have been successfully constructed against various antigens, for example, antibodies against IL-2 receptor as described in Queen *et al.*, 1989, Proc. Natl. Acad. Sci. USA 86:10029; 35 antibodies against the cell surface receptor CAMPATH as described in Riechmann *et al.*, 1988, Nature 332:323; antibodies against hepatitis B in Co *et al.*, 1991, Proc. Natl. Acad. Sci.

USA 88:2869; as well as against viral antigens of the respiratory syncytial virus in Tempest *et al.*, 1991, Bio-Technology 9:267. Humanized antibodies are most preferred for therapeutic use in humans.

Alternatively, techniques described for the production of single chain antibodies (U.S. 5 Patent 4,946,778; Bird, 1988, Science 242: 423-426; Huston *et al.*, 1988, Proc. Natl. Acad. Sci. USA 85: 5879-5883; and Ward *et al.*, 1989, Nature 334: 544-546) can be adapted to produce single chain antibodies against α 2M receptor or HSP- α 2M receptor complexes, or portions thereof. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide.

10 Antibody fragments that recognize specific epitopes may be generated by known techniques. For example, such fragments include but are not limited to: the $F(ab') fragments, which can be produced by pepsin digestion of the antibody molecule and the Fab fragments, which can be generated by reducing the disulfide bridges of the $F(ab') fragments. Alternatively, Fab expression libraries may be constructed (Huse *et al.*, 1989, Science, 246: 15 1275-1281) to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity.$$

Antibodies to the α 2M receptor can, in turn, be utilized to generate anti-idiotype antibodies that "mimic" the α 2M receptor, using techniques well known to those skilled in the art (see, *e.g.*, Greenspan & Bona, 1993, FASEB J 7(5):437-444; and Nissinoff, 1991, J. 20 Immunol. 147(8):2429-2438). For example antibodies which bind to the α 2M receptor ECD and competitively inhibit the binding of HSPs to the α 2M receptor can be used to generate anti-idiotypes that "mimic" the ECD and, therefore, bind and neutralize HSPs. Such 25 neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize the native ligand and treat HSP- α 2M receptor-related disorders, such as immunological disorders, proliferative disorders, and infectious diseases.

Alternatively, antibodies to the α 2M receptor that can act as agonists of the α 2M receptor activity can be generated. Such antibodies will bind to the α 2M receptor and activate the signal transducing activity of the receptor. In addition, antibodies that act as antagonist of the α 2M receptor activity, *i.e.* inhibit the activation of the α 2M receptor would 30 be particularly useful for treating autoimmune disorders, proliferative disorders, such as cancer, and infectious diseases. Methods for assaying for such agonists and antagonists are described in detail in Section 5.2, below.

5.2 ASSAYS FOR THE IDENTIFICATION OF COMPOUNDS THAT MODULATE HSP- α 2M RECEPTOR INTERACTIONS

The present invention is based on the discovery that the α 2M receptor recognizes HSP-antigenic peptide complexes and transports them within the cell for the purpose of presenting such antigenic molecules to cells of the immune system and eliciting an immune response. Thus, methods for identifying a molecule that enhances or blocks the function of the receptor are included in the invention. The present invention provides *in vitro* and *in vivo* assay systems, described in the subsections below, which can be used to identify compounds or compositions that modulate the activity of the α 2M receptor and its interaction with HSPs or HSP-peptide complexes. The invention provides screening methodologies useful in the identification of small molecules, proteins and other compounds which modulate the interaction of HSPs with the α 2M receptor. Such compounds may bind the α 2M receptor genes or gene products with differing affinities, and may serve as regulators of receptor activity *in vivo* with useful therapeutic applications in modulating the immune response. For example, certain compounds that inhibit receptor function may be used in patients to downregulate destructive immune responses which are caused by cellular release of HSPs.

Methods to screen potential agents for their ability to modulate α 2M receptor expression and activity can be designed based on the inventor's discovery of the receptor and its role in HSP or HSP-peptide complex binding and recognition. α 2M receptor protein, nucleic acids, and derivatives can be used in screening assays to detect molecules that specifically bind to HSP proteins, derivatives, or nucleic acids, and thus have potential use as agonists or antagonists of the α 2M receptor, to modulate the immune response. In a preferred embodiment, such assays are performed to screen for molecules with potential utility as anti-autoimmune disease, anti-cancer and anti-infective drugs (such as anti-viral drugs and antibiotic drugs), or lead compounds for drug development. For example, recombinant cells expressing α 2M receptor nucleic acids can be used to recombinantly produce α 2M receptor in these assays, to screen for molecules that interfere with the binding of HSPs to the α 2M receptor. Similar methods can be used to screen for molecules that bind to the α 2M receptor derivatives or nucleic acids. Methods that can be used to carry out the foregoing are commonly known in the art.

In one embodiment, an assay for identifying a compound that modulates an HSP- α 2M receptor-mediated process is disclosed. This assay comprises: (a) contacting a test compound with an HSP and an α 2M receptor; and (b) measuring the level of α 2M receptor activity or expression, such that if the level of activity or expression measured in (b) differs from the level of α 2M receptor activity in the absence of the test compound, then a compound that modulates an HSP- α 2M receptor-mediated process is identified. In another

embodiment, in which the compound identified is an antagonist which interferes with the interaction of the HSP with the α 2M receptor, the method further comprises the step of determining whether the level interferes with the interaction of the HSP and the α 2M receptor.

5 In another embodiment, a cell-based method for identifying a compound that modulates an HSP- α 2M receptor-mediated process is described. This method comprises the following steps: (a) contacting a test compound with a heat shock protein and an α 2M receptor-expressing cell; and (b) measuring the level of α 2M receptor activity or expression in the cell, such that if the level of activity or expression measured in (b) differs from the 10 level of α 2M receptor activity in the absence of the test compound, then a compound that modulates an HSP- α 2M receptor-mediated process is identified.

In another embodiment, a receptor-ligand binding assay for identifying a compound that modulates the binding of an HSP to the α 2M receptor, comprises: (a) contacting an HSP with an α 2M receptor, or fragment, or analog, derivative or mimetic thereof, in the presence 15 of a test compound; and (b) measuring the amount of heat shock protein bound to the α 2M receptor, or fragment, analog, derivative or mimetic thereof, such that if the amount of bound heat shock protein measured in (b) differs from the amount of bound heat shock protein measured in the absence of the test compound, then a compound that modulates the binding of an HSP to the α 2M receptor is identified.

20 In another embodiment, a method for identifying a compound that modulates heat shock protein-mediated antigen presentation by alpha (2) macroglobulin receptor-expressing cells comprises: (a) adding a test compound to a mixture of alpha (2) macroglobulin receptor-expressing cells and a complex consisting essentially of a heat shock protein noncovalently associated with an antigenic molecule, under conditions conducive to alpha (2) 25 macroglobulin receptor-mediated endocytosis; (b) measuring the level of stimulation of antigen-specific cytotoxic T cells by the alpha (2) macroglobulin receptor-expressing cells, such that if the level measured in (b) differs from the level of said stimulation in the absence of the test compound, then a compound that modulates heat shock protein-mediated antigen presentation by alpha (2) macroglobulin receptor-expressing cells is identified.

30 The assays of the present invention may be first optimized on a small scale (*i.e.*, in test tubes), and then scaled up for high-throughput assays. In various embodiments, the *in vitro* screening assays of the present invention may be performed using purified components or cell lysates. In other embodiments, the screening assays may be carried out in intact cells in culture and in animal models. In accordance with the present invention, test compounds 35 which are shown to modulate the activity of the α 2M receptor as described herein *in vitro*, will further be assayed *in vivo*, including cultured cells and animal models to determine if the

test compound has the similar effects *in vivo* and to determine the effects of the test compound on antigen presentation, cytokine release, intracellular Ca⁺⁺ release, T-cell cytotoxicity, tumor progression, the accumulation or degradation of positive and negative regulators, cellular proliferation, *etc.*

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5.2.1 α 2M RECEPTOR-LIGAND BINDING ASSAYS

The screening assays, described herein, can be used to identify compounds and compositions, including peptides and organic, non-protein molecules that modulate the interaction between HSPs and the α 2M receptor. Recombinant, synthetic, and otherwise 10 exogenous compounds may have binding capacity and, therefore, may be candidates for pharmaceutical agents. Alternatively, the proteins and compounds include endogenous cellular components which interact with the identified genes and proteins *in vivo*. Such endogenous components may provide new targets for pharmaceutical and therapeutic interventions.

15 Thus, in a preferred embodiment, both naturally occurring and/or synthetic compounds (*e.g.*, libraries of small molecules or peptides), may be screened for modulating α 2M receptor activity. In another series of embodiments, cell lysates or tissue homogenates may be screened for proteins or other compounds which bind to one of the normal or mutant α 2M receptor genes and α 2M receptor polypeptides.

20 The screening assays described herein may be used to identify small molecules, peptides or proteins, or derivatives, analogs and fragments thereof, that modulate the interaction of HSPs and the α 2M receptor. Such compounds may be used as agonists or antagonists of the uptake of HSPs and HSP complexes by the cell surface receptor. For example, compounds that modulate the HSP- α 2M receptor interaction include, but are not 25 limited to, compounds that bind to the α 2M receptor, thereby either inhibiting (antagonists) or enhancing (agonists) the binding of HSPs and HSP complexes to the receptor, as well as compounds that bind to HSPs, thereby preventing or enhancing binding of HSPs to the receptor. Compounds that affect α 2M gene activity (by affecting α 2M gene expression, including molecules, *e.g.*, proteins or small organic molecules, that affect transcription or 30 interfere with splicing events so that expression of the full length or truncated forms of α 2M can be modulated) can also be identified in the screens of the invention. Further, it should be noted that the assays described can also identify compounds that modulate HSP uptake by α 2M receptor (*e.g.*, compounds which affect downstream signaling in the α 2M receptor signal transduction pathway). The identification and use of such compounds which affect

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signaling events downstream of the α 2M receptor and thus modulate effects of the receptor on the immune response are within the scope of the invention.

Compounds that affect the α 2M receptor gene activity (by affecting the α 2M receptor gene expression, including molecules, *e.g.*, proteins or small organic molecules, that affect transcription or interfere with splicing events so that expression of the full length or the truncated form of the α 2M receptor can be modulated) can also be identified in the screens of the invention. However, it should be noted that the assays described can also identify compounds that modulate the α 2M receptor signal transduction (*e.g.*, compounds which affect downstream signaling events, such as inhibitors or enhancers of endocytic activity which is activated by ligand binding to the α 2M receptor). The identification and use of such compounds which affect signaling events downstream of the α 2M receptor and thus modulate effects of the α 2M receptor on the allergenic response are within the scope of the invention.

The screening assays described herein are designed to detect compounds that modulate, *i.e.* interfere with or enhance, HSP- α 2M receptor interactions. As described in detail below, such assays are functional assays, such as binding assays, that can be adapted to a high-throughput screening methodologies.

Binding assays can be used to identify compounds that modulate the interaction between HSPs and the α 2M receptor. In one aspect of the invention the screens may be designed to identify compounds that disrupt the interaction between the α 2M receptor and an HSP, such as, for example, peptides derived from an HSP, α 2M, or another α 2M receptor ligand. Such compounds will be useful as lead compounds for antagonists of HSP- α 2M receptor-related disorders and conditions, such as immune disorders, proliferative disorders, and infectious diseases.

Binding assays may be performed either as direct binding assays or as competition binding assays. In a direct binding assay, a test compound is tested for binding either to the α 2M receptor or to an HSP. Then, in a second step, the test compound is tested for its ability to modulate the HSP- α 2M receptor interaction. Competition binding assays, on the other hand, assess the ability of a test compound to compete with an HSP for binding to the α 2M receptor.

In a direct binding assay, either the HSP and/or the α 2M receptor is contacted with a test compound under conditions that allow binding of the test compound to the ligand or the receptor. The binding may take place in solution or on a solid surface. Preferably, the test compound is previously labeled for detection. Any detectable compound may be used for labeling, such as but not limited to, a luminescent, fluorescent, or radioactive isotope or group containing same, or a nonisotopic label, such as an enzyme or dye. After a period of

incubation sufficient for binding to take place, the reaction is exposed to conditions and manipulations that remove excess or non-specifically bound test compound. Typically, it involves washing with an appropriate buffer. Finally, the presence of an HSPs-test compound or a the α 2M receptor-test compound complex is detected.

5 In a competition binding assay, test compounds are assayed for their ability to disrupt or enhance the binding of the HSP to the α 2M receptor. Labeled HSP may be mixed with the α 2M receptor or fragment or derivative thereof, and placed under conditions in which the interaction between them would normally occur, with and without the addition of the test compound. The amount of labeled HSP that binds the α 2M receptor may be compared to the
10 amount bound in the presence or absence of test compound.

In a preferred embodiment, to facilitate complex formation and detection, the binding assay is carried out with one or more components immobilized on a solid surface. In various embodiments, the solid support could be, but is not restricted to, polycarbonate, polystyrene, polypropylene, polyethylene, glass, nitrocellulose, dextran, nylon, polyacrylamide
15 and agarose. The support configuration can include beads, membranes, microparticles, the interior surface of a reaction vessel such as a microtiter plate, test tube or other reaction vessel. The immobilization of the α 2M receptor, or other component, can be achieved through covalent or non-covalent attachments. In one embodiment, the attachment may be indirect, *i.e.* through an attached antibody. In another embodiment, the α 2M receptor and
20 negative controls are tagged with an epitope, such as glutathione S-transferase (GST) so that the attachment to the solid surface can be mediated by a commercially available antibody such as anti-GST (Santa Cruz Biotechnology).

For example, such an affinity binding assay may be performed using a the α 2M receptor which is immobilized to a solid support. Typically, the non-mobilized component
25 of the binding reaction, in this case either HSP or the test compound, is labeled to enable detection. A variety of labeling methods are available and may be used, such as luminescent, chromophore, fluorescent, or radioactive isotope or group containing same, and nonisotopic labels, such as enzymes or dyes. In a preferred embodiment, the test compound is labeled with a fluorophore such as fluorescein isothiocyanate (FITC, available from Sigma
30 Chemicals, St. Louis).

The labeled test compounds, or HSP plus test compounds, are then allowed to contact with the solid support, under conditions that allow specific binding to occur. After the binding reaction has taken place, unbound and non-specifically bound test compounds are separated by means of washing the surface. Attachment of the binding partner to the solid
35 phase can be accomplished in various ways known to those skilled in the art, including but not limited to chemical cross-linking, non-specific adhesion to a plastic surface, interaction

with an antibody attached to the solid phase, interaction between a ligand attached to the binding partner (such as biotin) and a ligand-binding protein (such as avidin or streptavidin) attached to the solid phase, and so on.

Finally, the label remaining on the solid surface may be detected by any detection 5 method known in the art. For example, if the test compound is labeled with a fluorophore, a fluorimeter may be used to detect complexes.

Preferably, the α 2M receptor is added to binding assays in the form of intact cells that 10 express the α 2M receptor, or isolated membranes containing the α 2M receptor. Thus, direct binding to the α 2M receptor or the ability of a test compound to modulate an HSP- α 2M receptor complex may be assayed in intact cells in culture or in animal models in the presence and absence of the test compound. A labeled HSP may be mixed with cells that 15 express the α 2M receptor, or to crude extracts obtained from such cells, and the test compound may be added. Isolated membranes may be used to identify compounds that interact with the α 2M receptor. For example, in a typical experiment using isolated membranes, cells may be genetically engineered to express the α 2M receptor. Membranes can be harvested by standard techniques and used in an *in vitro* binding assay. Labeled 20 ligand (e.g., 125 I-labeled HSP) is bound to the membranes and assayed for specific activity; specific binding is determined by comparison with binding assays performed in the presence of excess unlabeled (cold) ligand. Alternatively, soluble α 2M receptor may be recombinantly 25 expressed and utilized in non-cell based assays to identify compounds that bind to the α 2M receptor. The recombinantly expressed α 2M receptor polypeptides or fusion proteins containing the extracellular domain (ECD) of the α 2M receptor, or one or more subdomains thereof, can be used in the non-cell based screening assays. Alternatively, peptides corresponding to one or more of the CDs of the α 2M receptor, or fusion proteins containing 30 one or more of the CDs of the α 2M receptor can be used in non-cell based assay systems to identify compounds that bind to the cytoplasmic portion of the α 2M receptor; such compounds may be useful to modulate the signal transduction pathway of the α 2M receptor. In non-cell based assays the recombinantly expressed the α 2M receptor is attached to a solid 35 substrate such as a test tube, microtiter well or a column, by means well known to those in the art (see Ausubel *et al.*, *supra*). The test compounds are then assayed for their ability to bind to the α 2M receptor.

Alternatively, the binding reaction may be carried out in solution. In this assay, the labeled component is allowed to interact with its binding partner(s) in solution. If the size differences between the labeled component and its binding partner(s) permit such a 35 separation, the separation can be achieved by passing the products of the binding reaction through an ultrafilter whose pores allow passage of unbound labeled component but not of its

binding partner(s) or of labeled component bound to its partner(s). Separation can also be achieved using any reagent capable of capturing a binding partner of the labeled component from solution, such as an antibody against the binding partner, a ligand-binding protein which can interact with a ligand previously attached to the binding partner, and so on.

5 In a one embodiment, for example, a phage library can be screened by passing phage from a continuous phage display library through a column containing purified α 2M receptor, or derivative, analog, fragment, or domain, thereof, linked to a solid phase, such as plastic beads. By altering the stringency of the washing buffer, it is possible to enrich for phage that express peptides with high affinity for the α 2M receptor. Phage isolated from the column
10 can be cloned and the affinities of the short peptides can be measured directly. Sequences for more than one oligonucleotide can be combined to test for even higher affinity binding to the α 2M receptor. Knowing which amino acid sequences confer the strongest binding to the α 2M receptor, computer models can be used to identify the molecular contacts between the α 2M receptor and the test compound. This will allow the design of non-protein compounds
15 which mimic those contacts. Such a compound may have the same activity of the peptide and can be used therapeutically, having the advantage of being efficient and less costly to produce.

In another specific embodiment of this aspect of the invention, the solid support is membranes containing the α 2M receptor attached to a microtiter dish. Test compounds, for
20 example, cells that express library members are cultivated under conditions that allow expression of the library members in the microtiter dish. Library members that bind to the protein (or nucleic acid or derivative) are harvested. Such methods, are described by way of example in Parmley and Smith, 1988, Gene 73:305-318; Fowlkes *et al.*, 1992, BioTechniques 13:422-427; PCT Publication No. WO 94/18318; and in references cited
25 hereinabove.

In another embodiment of the present invention, interactions between the α 2M receptor or HSP and a test compound may be assayed *in vitro*. Known or unknown molecules are assayed for specific binding to the α 2M receptor nucleic acids, proteins, or derivatives under conditions conducive to binding, and then molecules that specifically bind
30 to the α 2M receptor are identified. The two components can be measured in a variety of ways. One approach is to label one of the components with an easily detectable label, place it together with a test component(s) under conditions that allow binding to occur, perform a separation step which separates bound labeled component from unbound labeled component, and then measure the amount of bound component. In one embodiment, the α 2M receptor
35 can be labeled and added to a test agent, using conditions that allow binding to occur.

Binding of the test agent can be determined using polyacrylamide gel analysis to compare complexes formed in the presence and absence of the test agent.

In yet another embodiment, binding of HSP to the α 2M receptor may be assayed in intact cells in animal models. A labeled HSP may be administered directly to an animal, with and without a test compound. Uptake of the HSP may be measured in the presence and the absence of test compound. For these assays, host cells to which the test compound is added may be genetically engineered to express the α 2M receptor and/or HSP, which may be transient, induced or constitutive, or stable. For the purposes of the screening methods of the present invention, a wide variety of host cells may be used including, but not limited to, tissue culture cells, mammalian cells, yeast cells, and bacteria. Mammalian cells such as macrophages or other cells that express the α 2M receptor, *i.e.*, cells of the monocytic lineage, liver parenchymal cells, fibroblasts, keratinocytes, neuronal cells, and placental syncytiotrophoblasts, may be a preferred cell type in which to carry out the assays of the present invention. Bacteria and yeast are relatively easy to cultivate but process proteins differently than mammalian cells.

5.2.2 α 2M RECEPTOR ACTIVITY ASSAYS

After identification of a test compound that modulates the interaction of HSP with the α 2M receptor, the test compound can be further characterized to measure its effect on α 2M receptor activity and the HSP- α 2M receptor endocytic signaling pathway. For example, the test compound may be characterized by testing its effect on HSP/ α 2M cellular activity *in vivo*. Such assays include downstream signaling assays, antigen presentation assays, assays for antigen-specific activation of cytotoxic T cells, and the like.

In various embodiments, a candidate compound identified in a primary assay may be tested for its effect on innate α 2M receptor signaling activity. For example, downstream signaling effects of α 2M receptor activation which can be assayed include, but are not limited to: enhanced locomotion and chemotaxis of macrophages (Forrester *et al.*, 1983, Immunology 50: 251-259), down regulation of proteinase synthesis, and elevation of intracellular calcium, inositol phosphates and cyclic AMP (Misra *et al.*, 1993, Biochem. J., 290:885-891). Other innate immune responses that can be tested are release of cytokines (*i.e.*, IL-12, IL1 β , GMCSF, and TNF α). Thus, as secondary assays, any identified candidate compound can be tested for changes in such activities in the presence and absence.

For example, in one embodiment, a chemotaxis assay can be used to further characterize a candidate identified by a primary screening assay. It is known that α 2M modified by protease interaction can induce directional migration of cells towards their ligand. A number of techniques can be used to test chemotactic migration *in vitro* (see, *e.g.*,

Leonard *et al.*, 1995, "Measurement of α and β Chemokines", in Current Protocols in Immunology, 6.12.1-6.12.28, Ed. Coligan *et al.*, John Wiley & Sons, Inc. 1995). For example, in one embodiment, a candidate compound can be tested for its ability to modulate the ability of alpha (2) macroglobulin receptor to induce migration of cells that express the receptor using a chemokine gradient in a multiwell Boyden chemotaxis chamber. In a specific example of this method, a serial dilution of an HSP/ alpha (2) macroglobulin receptor antagonist or agonist test compound identified in the primary screen is placed in the bottom wells of the Boyden chemotaxis chamber. A constant amount of HSP is also added to the dilution series. As a control, at least one aliquot contains only HSP. The contribution of the antagonist or agonist compound to the chemotactic activity of alpha (2) macroglobulin receptor is measured by comparing number of migrating cells on the lower surface of the membrane filter of the aliquots containing only HSP, with the number of cells in aliquots containing test compound and HSP. If addition of the test compound to the HSP solution results in a decrease in the number of cells detected the membrane relative to the number of cells detected using a solution containing only HSP, then an antagonist of HSP induction of chemotactic activity of alpha (2) macroglobulin receptor-expressing cells is identified.

Elevation in intracellular ionized calcium concentration ($[Ca^{2+}]$) is also an indicator of α 2M receptor activation (Misra *et al.*, 1993, *supra*). Thus, in another embodiment, calcium flux assays can be used as secondary screens to further characterize modulators of HSP/ α 2M receptor interactions. Intracellular calcium ion concentration can be measured in cells that express the α 2M receptor in the presence of the HSP, in the presence and the absence of a test compound. For example, calcium mobilization can be detected and measured by flow cytometry, by labeling with fluorescent dyes that are trapped intracellularly. A fluorescent dye such as Indo-1 exhibits a change in emission spectrum upon binding calcium, the ratio of fluorescence produced by the calcium-bound dye to that produced by the unbound dye may be used to estimate the intracellular calcium concentration. In a specific embodiment, cells are incubated in a cuvette in media containing Indo-1 at 37°C and are excited, and fluorescence is measured using a fluorimeter (Photon Technology Corporation, International). HSP is added at a specific time point, in the presence and the absence of a test compound, EGTA is added to the cuvette to release and chelate total calcium, and the response is measured. Binding of HSP ligand results in increased intracellular Ca^{2+} concentration in cells that express alpha (2) macroglobulin receptor. An agonist results in a relative increased intracellular Ca^{2+} concentration, whereas an antagonist results in a relative decreased intracellular Ca^{2+} concentration.

In other embodiments, antigen-specific response assays may be used to detect the effect of a candidate compound on presentation of antigenic molecule by HSP. For example,

an antigen presentation assay may be performed to determine the effect of a compound *in vivo* on the uptake of HSP-antigenic molecules by cells expressing the α 2M receptor. Such re-presentation assays are known in the art, and have been described previously (Suto and Srivastava, 1995, Science 269:1585-1588). For example, in one embodiment, antigen 5 presenting cells, such as a macrophage cell line (*e.g.*, RAW264.7), are mixed with antigen-specific T cells in media, using approximately 10,000 cells of each type at approximately a 1:1 ratio. Complexes of HSP (10 μ g/ml) and a peptide antigen, as well as test compound, is added to the cells and the culture is incubated for approximately 20 hours. Stimulation of T cells may then be measured in the presence and absence of test compound.

10 In another embodiment, antigen-specific T cell stimulation may be assayed. In one embodiment an IFN- γ release assay may be used. After washing, cells are fixed, permeabilized, and reacted with dye-labeled antibodies reactive with human IFN- γ (PE- anti-IFN- γ). Samples are analyzed by flow cytometry using standard techniques. Alternatively, a 15 filter immunoassay, ELISA (enzyme linked immunosorbent assay), or enzyme-linked immunospot assay (ELISPOT) assay, may be used to detect specific cytokines produced by an activated T cell. In one embodiment, for example, a nitrocellulose-backed microtiter plate is coated with a purified cytokine-specific primary antibody, *i.e.*, anti-IFN- γ , and the plate is blocked to avoid background due to nonspecific binding of other proteins. A sample of APC 20 cells stimulated with antigen is diluted onto the wells of the microtiter plate. A labeled, *e.g.*, biotin-labeled, secondary anti-cytokine antibody is added. The antibody cytokine complex can then be detected, *i.e.*, by enzyme-conjugated streptavidin – cytokine-secreting cells will appear as “spots” by visual, microscopic, or electronic detection methods. In another embodiment, “tetramer staining” assay (Altman *et al.*, 1996, Science 274: 94-96) may be used to identify antigen-specific T-cells. For example, an MHC molecule containing a 25 specific peptide antigen, such as a tumor-specific antigen, is multimerized to make soluble peptide tetramers and labeled, for example, by complexing to streptavidin. The MHC-peptide antigen complex is then mixed with a population of stimulated T cells. Biotin is then used to stain T cells which recognize and bind to the MHC-antigen complex.

30 5.2.3 COMPOUNDS THAT CAN BE SCREENED IN ACCORDANCE WITH THE INVENTION

The screening assays described herein may be used to identify small molecules, peptides or proteins, or derivatives, analogs and fragments thereof, that modulate the interaction of the HSP with the α 2M receptor. The compounds which may be screened in accordance with the invention include, but are not limited to small molecules, peptides, 35 antibodies and fragments thereof, and other organic compounds (*e.g.*, peptidomimetics) that

bind to the ECD of the α 2M receptor and either inhibit the activity triggered by the natural ligand (*i.e.*, antagonists) or mimic the activity triggered by the natural ligand (*i.e.*, agonists), as well as small molecules, peptides, antibodies or fragments thereof, and other organic compounds. In one embodiment, such compounds include sequences of the α 2M receptor, 5 such as the ECD of the α 2M receptor (or a portion thereof), which can bind to and "neutralize" natural ligands, such as HSPs, α 2M, LDL, *etc.* In another embodiment, such compounds include ligand sequences, such as HSP sequences and/or α 2M sequences, which can bind to the active site of the α 2M receptor, and block its activity.

Compounds that may be used for screening include, but are not limited to, peptides 10 such as, for example, soluble peptides, including but not limited to members of random peptide libraries; (see, *e.g.*, Lam *et al.*, 1991, *Nature* 354:82-84; Houghten *et al.*, 1991, *Nature* 354:84-86), and combinatorial chemistry-derived molecular library made of D- and/or L- configuration amino acids, phosphopeptides (including, but not limited to, members of random or partially degenerate, directed phosphopeptide libraries; see, *e.g.*, Songyang *et al.*, 15 1993, *Cell* 72:767-778), antibodies (including, but not limited to, polyclonal, monoclonal, humanized, anti-idiotypic, chimeric or single chain antibodies, and FAb, F(ab')₂ and FAb expression library fragments, and epitope-binding fragments thereof), and small organic or inorganic molecules.

In one embodiment of the present invention, peptide libraries may be used as a source 20 of test compounds that can be used to screen for modulators of HSP- α 2M receptor interactions. Diversity libraries, such as random or combinatorial peptide or nonpeptide libraries can be screened for molecules that specifically bind to the α 2M receptor. Many libraries are known in the art that can be used, *e.g.*, chemically synthesized libraries, recombinant (*e.g.*, phage display libraries), and *in vitro* translation-based libraries.

25 Examples of chemically synthesized libraries are described in Fodor *et al.*, 1991, *Science* 251:767-773; Houghten *et al.*, 1991, *Nature* 354:84-86; Lam *et al.*, 1991, *Nature* 354:82-84; Medynski, 1994, *Bio/Technology* 12:709-710; Gallop *et al.*, 1994, *J. Medicinal Chemistry* 37(9):1233-1251; Ohlmeyer *et al.*, 1993, *Proc. Natl. Acad. Sci. USA* 90:10922-10926; Erb *et al.*, 1994, *Proc. Natl. Acad. Sci. USA* 91:11422-11426; Houghten *et al.*, 1992, *Biotechniques* 13:412; Jayawickreme *et al.*, 1994, *Proc. Natl. Acad. Sci. USA* 91:1614-1618; Salmon *et al.*, 1993, *Proc. Natl. Acad. Sci. USA* 90:11708-11712; PCT 30 Publication No. WO 93/20242; and Brenner and Lerner, 1992, *Proc. Natl. Acad. Sci. USA* 89:5381-5383.

Examples of phage display libraries are described in Scott & Smith, 1990, 35 *Science* 249:386-390; Devlin *et al.*, 1990, *Science*, 249:404-406; Christian *et al.*, 1992, *J.*

Mol. Biol. 227:711-718; Lenstra, 1992, J. Immunol. Meth. 152:149-157; Kay *et al.*, 1993, Gene 128:59-65; and PCT Publication No. WO 94/18318 dated August 18, 1994.

By way of examples of nonpeptide libraries, a benzodiazepine library (*see e.g.*, Bunin *et al.*, 1994, Proc. Natl. Acad. Sci. USA 91:4708-4712) can be adapted for use. Peptoid 5 libraries (Simon *et al.*, 1992, Proc. Natl. Acad. Sci. USA 89:9367-9371) can also be used. Another example of a library that can be used, in which the amide functionalities in peptides have been permethylated to generate a chemically transformed combinatorial library, is described by Ostresh *et al.* (1994, Proc. Natl. Acad. Sci. USA 91:11138-11142).

Screening the libraries can be accomplished by any of a variety of commonly known 10 methods. See, *e.g.*, the following references, which disclose screening of peptide libraries: Parmley & Smith, 1989, Adv. Exp. Med. Biol. 251:215-218; Scott & Smith, 1990, Science 249:386-390; Fowlkes *et al.*, 1992; BioTechniques 13:422-427; Oldenburg *et al.*, 1992, Proc. Natl. Acad. Sci. USA 89:5393-5397; Yu *et al.*, 1994, Cell 76:933-945; Staudt *et al.*, 1988, Science 241:577-580; Bock *et al.*, 1992, Nature 355:564-566; Tuerk *et al.*, 1992, 15 Proc. Natl. Acad. Sci. USA 89:6988-6992; Ellington *et al.*, 1992, Nature 355:850-852; U.S. Patent No. 5,096,815, U.S. Patent No. 5,223,409, and U.S. Patent No. 5,198,346, all to Ladner *et al.*; Rebar & Pabo, 1993, Science 263:671-673; and PCT Publication No. WO 94/18318.

In another embodiment of the present invention, the screening may be performed by 20 adding the labeled HSP to *in vitro* translation systems such as a rabbit reticulocyte lysate (RRL) system and then proceeding with *in vitro* priming reaction. *In vitro* translation-based libraries include but are not limited to those described in PCT Publication No. WO 91/05058 dated April 18, 1991; and Mattheakis *et al.*, 1994, Proc. Natl. Acad. Sci. USA 91:9022-9026.

Compounds that can be tested and identified methods described herein can include, 25 but are not limited to, compounds obtained from any commercial source, including Aldrich (Milwaukee, WI 53233), Sigma Chemical (St. Louis, MO), Fluka Chemie AG (Buchs, Switzerland) Fluka Chemical Corp. (Ronkonkoma, NY), Eastman Chemical Company, Fine Chemicals (Kingsport, TN), Boehringer Mannheim GmbH (Mannheim, Germany), Takasago (Rockleigh, NJ), SST Corporation (Clifton, NJ), Ferro (Zachary, LA 70791), Riedel-deHaen 30 Aktiengesellschaft (Seelze, Germany), PPG Industries Inc., Fine Chemicals (Pittsburgh, PA 15272). Further any kind of natural products may be screened using the methods of the invention, including microbial, fungal, plant or animal extracts.

Furthermore, diversity libraries of test compounds, including small molecule test 35 compounds, may be utilized. For example, libraries may be commercially obtained from Specs and BioSpecs B.V. (Rijswijk, The Netherlands), Chembridge Corporation (San Diego, CA), Contract Service Company (Dolgoprudny, Moscow Region, Russia), Comgenex USA

Inc. (Princeton, NJ), Maybridge Chemicals Ltd. (Cornwall PL34 OHW, United Kingdom), and Asinex (Moscow, Russia).

Still further, combinatorial library methods known in the art, can be utilize, including, but not limited to: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the "one-bead one-compound" library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, 1997, *Anticancer Drug Des.* 12:145). Combinatorial libraries of test compounds, including small molecule test compounds, can be utilized, and may, for example, be generated as disclosed in Eichler & Houghten, 1995, *Mol. Med. Today* 1:174-180; Dolle, 1997, *Mol. Divers.* 2:223-236; and Lam, 1997, *Anticancer Drug Des.* 12:145-167.

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt *et al.*, 1993, *Proc. Natl. Acad. Sci. USA* 90:6909; Erb *et al.*, 1994, *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann *et al.*, 1994, *J. Med. Chem.* 37:2678; Cho *et al.*, 1993, *Science* 261:1303; Carell *et al.*, 1994, *Angew. Chem. Int. Ed. Engl.* 33:2059; Carell *et al.*, 1994, *Angew. Chem. Int. Ed. Engl.* 33:2061; and Gallop *et al.*, 1994, *J. Med. Chem.* 37:1233.

Libraries of compounds may be presented in solution (e.g., Houghten, 1992, *BioTechniques* 13:412-421), or on beads (Lam, 1991, *Nature* 354:82-84), chips (Fodor, 1993, *Nature* 364:555-556), bacteria (U.S. Patent No. 5,223,409), spores (Patent Nos. 5,571,698; 5,403,484; and 5,223,409), plasmids (Cull *et al.*, 1992, *Proc. Natl. Acad. Sci. USA* 89:1865-1869) or phage (Scott and Smith, 1990, *Science* 249:386-390; Devlin, 1990, *Science* 249:404-406; Cwirla *et al.*, 1990, *Proc. Natl. Acad. Sci. USA* 87:6378-6382; and Felici, 1991, *J. Mol. Biol.* 222:301-310).

Screening the libraries can be accomplished by any of a variety of commonly known methods. See, e.g., the following references, which disclose screening of peptide libraries: Parmley & Smith, 1989, *Adv. Exp. Med. Biol.* 251:215-218; Scott & Smith, 1990, *Science* 249:386-390; Fowlkes *et al.*, 1992; *BioTechniques* 13:422-427; Oldenburg *et al.*, 1992, *Proc. Natl. Acad. Sci. USA* 89:5393-5397; Yu *et al.*, 1994, *Cell* 76:933-945; Staudt *et al.*, 1988, *Science* 241:577-580; Bock *et al.*, 1992, *Nature* 355:564-566; Tuerk *et al.*, 1992, *Proc. Natl. Acad. Sci. USA* 89:6988-6992; Ellington *et al.*, 1992, *Nature* 355:850-852; U.S. Patent No. 5,096,815, U.S. Patent No. 5,223,409, and U.S. Patent No. 5,198,346, all to Ladner *et al.*; Rebar & Pabo, 1993, *Science* 263:671-673; and PCT Publication No. WO 94/18318.

5.3 IDENTIFICATION OF FRAGMENTS OF THE α 2M RECEPTOR AND/OR HSPs USEFUL FOR IMMUNOTHERAPY

The invention also encompasses methods for identifying HSP-binding α 2M receptor fragments (“HSP-binding domains”), and analogs, muteins, or derivatives thereof, which are capable of binding to, and uptake of, HSP-antigenic peptide complexes. Such HSP-binding domains can then be tested for activity *in vivo* and *in vitro* using the α 2M receptor/ligand binding assays, described in Section 5.2.1, above. In one embodiment, such a method for identifying an α 2M receptor fragment capable of binding a heat shock protein comprises the steps of: (a) contacting a heat shock protein with one or more alpha (2) macroglobulin receptor fragments; and (b) identifying an α 2M receptor polypeptide fragment which specifically binds to the heat shock protein.

HSP-binding domains of the alpha (2) macroglobulin receptor capable of binding HSP-antigenic peptide complexes, and can be further tested for activity using either *in vivo* binding assays, re-presentation assays, or CTL assays, such as those described in Section 5.2.2, above. For example, one such method for identifying an α 2M receptor fragment capable of inducing an HSP- α 2M receptor-mediated process comprises the steps of: (a) contacting a heat shock protein with cell expressing α 2M receptor fragment; and (b) measuring the level of alpha (2) macroglobulin receptor activity in the cell, such that if the level of the HSP- α 2M receptor-mediated process or activity measured in (b) is greater than the level of alpha (2) macroglobulin receptor activity in the absence of the α 2M receptor fragment, then an α 2M receptor fragment capable of inducing an HSP- α 2M receptor-mediated process is identified. Depending on their behavior in such assays, such molecules can be used to either enhance or, alternatively, block the function of the receptor when administered or expressed *in vivo*. For example, these assays can be used to identify α 2M receptor HSP-binding domains which can bind HSP-antigen complexes and negatively interfere with their uptake by antigen presenting cells. These antagonists could be used to downregulate immune responses which are caused by cellular release of HSPs. Alternatively, certain α 2M receptor HSP-binding domains may be used to enhance HSP-antigen complex uptake and signaling. Such agonists could be administered or expressed in subjects to elicit an immune response against an antigen of interest.

In another embodiment, the invention encompasses methods for identifying HSP fragments which are capable of binding and being taken up by the α 2M receptor (“ α 2M receptor-binding domains”), and analogs, muteins, or derivatives thereof. As described for assays for α 2M receptor-related polypeptides described above, such α 2M receptor-binding domains can then be tested for activity *in vivo* and *in vitro* using the binding assays described

in Section 5.2.1, above. For example, one such method for identifying a heat shock protein fragment capable of binding an α 2M receptor comprises: (a) contacting an α 2M receptor with one or more heat shock protein fragments; and (b) identifying a heat shock protein fragment which specifically binds to the α 2M receptor.

5 HSP fragments of interest may be further tested in cells, using *in vivo* binding assays, re-presentation assays, or CTL assays, such as those described in Section 5.2.2, above. For example, in one embodiment, such a method for identifying a heat shock protein fragment capable of inducing an HSP- α 2M receptor-mediated process comprises: a) contacting an α 2M receptor fragment with a cell expressing a heat shock protein; and b) measuring the
10 level of alpha (2) macroglobulin receptor activity in the cell, such that if the level of the HSP- α 2M receptor-mediated process or activity measured in (b) is greater than the level of alpha (2) macroglobulin receptor activity in the absence of said heat shock protein fragment.
Alternatively, α 2M receptor-binding domains which decrease uptake of HSPs could be used
15 to block HSP uptake by the α 2M receptor. In one embodiment, such HSP fragments comprising α 2M receptor-binding domain sequences could be used to construct recombinant fusion proteins, comprised of a heat shock protein α 2M receptor-binding domain and an antigenic peptide sequence. Such recombinant fusion proteins may be used to elicit an immune response and to treat or prevent immune diseases and disorders (Suzue *et al.*, 1997, Proc. Natl. Acad. Sci. U.S.A. 94: 13146-51).

20 The α 2M receptor fragments, analogs, muteins, and derivatives and/or HSP fragments, analogs, muteins, and derivatives of the invention may be produced by recombinant DNA techniques, synthetic methods, or by enzymatic or chemical cleavage of native α 2M receptor and/or HSPs.

Any eukaryotic cell may serve as the nucleic acid source for obtaining the coding
25 region of an α 2M receptor or HSP gene. Nucleic acid sequences encoding HSPs and/or the α 2M receptor can be isolated from vertebrate, mammalian, as well as primate sources, including humans. Amino acid sequences and nucleotide sequences of naturally occurring HSPs and α 2M receptor are generally available in sequence databases, such as Genbank.

The DNA may be obtained by standard procedures known in the art by DNA
30 amplification or molecular cloning directly from a tissue, cell culture, or cloned DNA (e.g., a DNA "library"). Clones derived from genomic DNA may contain regulatory and intron DNA regions in addition to coding regions; clones derived from cDNA will contain only exon sequences. In a preferred embodiment, DNA can be amplified from genomic or cDNA by polymerase chain reaction (PCR) amplification using primers designed from the known
35 sequence of an HSP or α 2M receptor. The polymerase chain reaction (PCR) is commonly used for obtaining genes or gene fragments of interest. For example, a nucleotide sequence

encoding a fragment of any desired length can be generated using PCR primers that flank the nucleotide sequence encoding the peptide-binding domain. Alternatively, an HSP or α 2M receptor gene sequence can be cleaved at appropriate sites with restriction endonuclease(s) if such sites are available, releasing a fragment of DNA encoding the peptide-binding domain.

5 If convenient restriction sites are not available, they may be created in the appropriate positions by site-directed mutagenesis and/or DNA amplification methods known in the art (see, for example, Shankarappa *et al.*, 1992, PCR Method Appl. 1:277-278). The DNA fragment that encodes a fragment of the HSP or α 2M receptor gene is then isolated, and ligated into an appropriate expression vector, care being taken to ensure that the proper

10 translation reading frame is maintained. Alternatives to isolating the genomic DNA include, but are not limited to, chemically synthesizing the gene sequence itself from a known sequence or making cDNA to the mRNA which encodes the HSP and/or α 2M receptor.

Any technique for mutagenesis known in the art can be used to modify individual nucleotides in a DNA sequence, for purpose of making amino acid substitution(s) in the 15 expressed peptide sequence, or for creating/deleting restriction sites to facilitate further manipulations. Such techniques include but are not limited to, chemical mutagenesis, *in vitro* site-directed mutagenesis (Hutchinson, C., *et al.*, 1978, J. Biol. Chem 253:6551), oligonucleotide-directed mutagenesis (Smith, 1985, Ann. Rev. Genet. 19:423-463; Hill *et al.*, 1987, Methods Enzymol. 155:558-568), PCR-based overlap extension (Ho *et al.*, 1989, Gene 20 77:51-59), PCR-based megaprimer mutagenesis (Sarkar *et al.*, 1990, Biotechniques, 8:404-407), etc. Modifications can be confirmed by double stranded dideoxy DNA sequencing.

An alternative to producing HSP and/or α 2M receptor fragments by recombinant techniques is peptide synthesis. For example, a peptide corresponding to a portion of an HSP and/or α 2M receptor comprising the substrate-binding domain, or which binds peptides *in vitro*, can be synthesized by use of a peptide synthesizer. Conventional peptide synthesis 25 may be used or other synthetic protocols well known in the art.

In addition, analogs and derivatives of HSP and/or α 2M receptor can be chemically synthesized. Furthermore, if desired, nonclassical amino acids or chemical amino acid 30 analogs can be introduced as a substitution or addition into the HSP and/or α 2M receptor sequence. Non-classical amino acids include but are not limited to the D-isomers of the common amino acids, α -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, γ -Abu, ϵ -Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, β -alanine, fluoro-amino acids, 35 designer amino acids such as β -methyl amino acids, C α -methyl amino acids, N α -methyl amino acids, and amino acid analogs in general.

HSP and/or α 2M receptor peptides, or a mutant or derivative thereof, may be synthesized by solid-phase peptide synthesis using procedures similar to those described by Merrifield, 1963, J. Am. Chem. Soc., 85:2149. During synthesis, N- α -protected amino acids having protected side chains are added stepwise to a growing polypeptide chain linked by its C-terminal and to an insoluble polymeric support i.e., polystyrene beads. The peptides are synthesized by linking an amino group of an N- α -deprotected amino acid to an α -carboxyl group of an N- α -protected amino acid that has been activated by reacting it with a reagent such as dicyclohexylcarbodiimide. The attachment of a free amino group to the activated carboxyl leads to peptide bond formation. The most commonly used N- α -protecting groups include Boc which is acid labile and Fmoc which is base labile. Details of appropriate chemistries, resins, protecting groups, protected amino acids and reagents are well known in the art and so are not discussed in detail herein (See, Atherton, *et al.*, 1989, Solid Phase Peptide Synthesis: A Practical Approach, IRL Press, and Bodanszky, 1993, Peptide Chemistry, A Practical Textbook, 2nd Ed., Springer-Verlag).

Purification of the resulting fragment is accomplished using conventional procedures, such as preparative HPLC using gel permeation, partition and/or ion exchange chromatography. The choice of appropriate matrices and buffers are well known in the art and so are not described in detail herein.

In an alternative embodiment, fragments of an HSP or the α 2M receptor may be obtained by chemical or enzymatic cleavage of native or recombinant HSP and/or α 2M receptor molecules. Specific chemical cleavage can be performed by cyanogen bromide, NaBH₄, acetylation, formylation, oxidation, reduction, metabolic synthesis in the presence of tunicamycin, *etc.*. Endoproteases that cleave at specific sites can also be used. Such proteases are known in the art, including, but not limited to, trypsin, α -chymotrypsin, V8 protease, papain, and proteinase K (see Ausubel *et al.*, (eds.), in "Current Protocols in Molecular Biology", Greene Publishing Associates and Wiley Interscience, New York, 17.4.6-17.4.8). The HSP and/or α 2M receptor amino acid sequence of interest can be examined for the recognition sites of these proteases. An enzyme is chosen which can release a peptide-binding domain or peptide-binding fragment. The HSP and/or α 2M receptor molecule is then incubated with the protease, under conditions that allow digestion by the protease and release of the specifically designated peptide-binding fragments. Alternatively, such protease digestions can be carried out blindly, *i.e.*, not knowing which digestion product will contain the peptide-binding domain, using specific or general specificity proteases, such as proteinase K or pronase.

Once a fragment is prepared, the digestion products may be purified as described above, and subsequently tested for the ability to bind peptide or for immunogenicity.

Methods for determining the immunogenicity of HSP complexes by cytotoxicity tests are described in Section 5.2.2.

5

5.4 DRUG DESIGN

Upon identification of a compound that modulates the interaction of the HSP with the α 2M receptor, such a compound can be further investigated to test for an ability to alter the immune response. In particular, for example, the compounds identified via the present 10 methods can be further tested *in vivo* in accepted animal models of HSP- α 2M receptor-mediated processes and HSP- α 2M receptor related disorders, such as, *e.g.*, immune disorders, proliferative disorders, and infectious diseases.

Computer modeling and searching technologies permit identification of compounds, or the improvement of already identified compounds, which can modulate the interaction of 15 an HSP with the α 2M receptor. Having identified such a compound or composition, the active sites or regions are identified. Such active sites might typically be ligand binding sites. The active site can be identified using methods known in the art including, for example, from the amino acid sequences of peptides, from the nucleotide sequences of nucleic acids, or from study of complexes of the relevant compound or composition with its natural ligand. In 20 the latter case, chemical or X-ray crystallographic methods can be used to find the active site by finding where on the factor the complexed ligand is found.

Next, the three dimensional geometric structure of the active site is determined. This can be done by known methods, including X-ray crystallography, which can determine a complete molecular structure. On the other hand, solid or liquid phase NMR can be used to 25 determine certain intra-molecular distances. Any other experimental method of structure determination can be used to obtain partial or complete geometric structures. The geometric structures may be measured with a complexed ligand, natural or artificial, which may increase the accuracy of the active site structure determined.

If an incomplete or insufficiently accurate structure is determined, the methods of 30 computer based numerical modeling can be used to complete the structure or improve its accuracy. Any recognized modeling method may be used, including parameterized models specific to particular biopolymers such as proteins or nucleic acids, molecular dynamics models based on computing molecular motions, statistical mechanics models based on thermal ensembles, or combined models. For most types of models, standard molecular force 35 fields, representing the forces between constituent atoms and groups, are necessary, and can

be selected from force fields known in physical chemistry. The incomplete or less accurate experimental structures can serve as constraints on the complete and more accurate structures computed by these modeling methods.

Finally, having determined the structure of the active site, either experimentally, by 5 modeling, or by a combination, candidate modulating compounds can be identified by searching databases containing compounds along with information on their molecular structure. Such a search seeks compounds having structures that match the determined active site structure and that interact with the groups defining the active site. Such a search can be manual, but is preferably computer assisted. These compounds found from this search are 10 potential the α 2M receptor-modulating compounds.

Alternatively, these methods can be used to identify improved modulating compounds from an already known modulating compound or ligand. The composition of the known compound can be modified and the structural effects of modification can be determined using the experimental and computer modeling methods described above applied to the new 15 composition. The altered structure is then compared to the active site structure of the compound to determine if an improved fit or interaction results. In this manner systematic variations in composition, such as by varying side groups, can be quickly evaluated to obtain modified modulating compounds or ligands of improved specificity or activity.

Further experimental and computer modeling methods useful to identify modulating 20 compounds based upon identification of the active sites of either the α 2M receptor or the HSP, and related ligands and their analogs, will be apparent to those of skill in the art.

Examples of molecular modeling systems are the CHARMM and QUANTA programs (Polygen Corporation, Waltham, MA). CHARMM performs the energy minimization and molecular dynamics functions. QUANTA performs the construction, 25 graphic modelling and analysis of molecular structure. QUANTA allows interactive construction, modification, visualization, and analysis of the behavior of molecules with each other.

A number of articles review computer modeling of drugs interactive with specific proteins, such as Rotivinen *et al.* (1988, *Acta Pharmaceutical Fennica* 97:159-166); Ripka 30 (1988 *New Scientist* 54-57); McKinlay and Rossmann (1989, *Annu. Rev. Pharmacol. Toxicol.* 29:111-122); Perry and Davies, OSAR: Quantitative Structure-Activity Relationships in Drug Design pp. 189-193 Alan R. Liss, Inc. 1989; Lewis and Dean (1989, *Proc. R. Soc. Lond.* 236:125-140 and 141-162); and, with respect to a model receptor for nucleic acid components, Askew *et al.* (1989, *J. Am. Chem. Soc.* 111:1082-1090). Other 35 computer programs that screen and graphically depict chemicals are available from companies such as BioDesign, Inc. (Pasadena, CA.), Allelix, Inc. (Mississauga, Ontario,

Canada), and Hypercube, Inc. (Cambridge, Ontario). Although these are primarily designed for application to drugs specific to particular proteins, they can be adapted to design of drugs specific to regions of DNA or RNA, once that region is identified.

5 5.5 DIAGNOSTIC USES

The α 2M receptor is a cell surface protein present on many tissues and cell types (Herz *et al.*, 1988, EMBO J. 7:4119-27; Moestrup *et al.*, 1992, Cell Tissue Res. 269: 375-82), that appears to be involved in the specific uptake and re-presentation of HSPs and HSP-peptide complexes. The α 2M receptor was initially identified as a heat shock protein
10 receptor due to its interaction with gp96, which is exclusively intracellular and is released as a result of necrotic but not apoptotic cell death. Thus, gp96 uptake by the α 2M receptor may act as a sensor of necrotic cell death. As such, HSP- α 2M receptor complexes may be used to detect and diagnose proliferative disorders, such as cancer, autoimmune disorders and infectious disease. Therefore, α 2M receptor proteins, analogues, derivatives, and
15 subsequences thereof, α 2M receptor nucleic acids (and sequences complementary thereto), and anti- α 2M receptor antibodies, have uses in detecting and diagnosing such disorders.

The α 2M receptor and α 2M receptor nucleic acids can be used in assays to detect, prognose, or diagnose immune system disorders that may result in tumorigenesis, carcinomas, adenomas etc, and viral disease.

20 The molecules of the present invention can be used in assays, such as immunoassays, to detect, prognose, diagnose, or monitor various conditions, diseases, and disorders affecting α 2M receptor expression, or monitor the treatment thereof. In particular, such an immunoassay is carried out by a method comprising contacting a sample derived from a patient with an HSP- α 2M receptor specific antibody under conditions such that
25 immunospecific binding can occur, and detecting or measuring the amount of any immunospecific binding by the antibody. In a specific aspect, such binding of antibody, in tissue sections, can be used to detect aberrant α 2M receptor localization or aberrant (e.g., low or absent) levels of α 2M receptor. In a specific embodiment, antibody to the α 2M receptor can be used to assay a patient tissue or serum sample for the presence of the α 2M receptor
30 where an aberrant level of α 2M receptor is an indication of a diseased condition. By "aberrant levels," is meant increased or decreased levels relative to that present, or a standard level representing that present, in an analogous sample from a portion of the body or from a subject not having the disorder.

35 The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, immunohisto-

chemistry radioimmunoassays, ELISA, "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few.

5 α 2M receptor genes and related nucleic acid sequences and subsequences, including complementary sequences, can also be used in hybridization assays. α 2M receptor nucleic acid sequences, or subsequences thereof, comprising about at least 8 nucleotides, can be used as hybridization probes. Hybridization assays can be used to detect, prognose, diagnose, or monitor conditions, disorders, or disease states associated with aberrant changes in α 2M
10 receptor expression and/or activity as described *supra*. In particular, such a hybridization assay is carried out by a method comprising contacting a sample containing nucleic acid with a nucleic acid probe capable of hybridizing to α 2M receptor DNA or RNA, under conditions such that hybridization can occur, and detecting or measuring any resulting hybridization.

15 In specific embodiments, diseases and disorders involving decreased immune responsiveness during an infection or malignant disorder can be diagnosed, or their suspected presence can be screened for, or a predisposition to develop such disorders can be detected, by detecting decreased levels of α 2M receptor protein, α 2M receptor RNA, or the α 2M receptor functional activity (*e.g.*, binding to HSP, antibody-binding activity *etc.*), or by detecting mutations in α 2M receptor RNA, DNA or α 2M receptor protein (*e.g.*,
20 translocations in the α 2M receptor nucleic acids, truncations in the α 2M receptor gene or protein, changes in nucleotide or amino acid sequence relative to wild-type α 2M receptor) that cause decreased expression or activity of α 2M receptor. Such diseases and disorders include but are not limited to those described in Sections 5.7, 5.8, and 5.9. By way of example, levels of the α 2M receptor protein can be detected by immunoassay, levels of α 2M
25 receptor RNA can be detected by hybridization assays (*e.g.*, Northern blots, *in situ*-hybridization), α 2M receptor activity can be assayed by measuring binding activities in vivo or *in vitro*. Translocations, deletions, and point mutations in α 2M receptor nucleic acids can be detected by Southern blotting, FISH, RFLP analysis, SSCP, PCR using primers, preferably primers that generate a fragment spanning at least most of the α 2M receptor gene, sequencing
30 of α 2M receptor genomic DNA or cDNA obtained from the patient, *etc.*

35 In a preferred embodiment, levels of α 2M receptor mRNA or protein in a patient sample are detected or measured relative to the levels present in an analogous sample from a subject not having the malignancy or hyperproliferative disorder. Decreased levels indicate that the subject may develop, or have a predisposition to developing, viral infection, malignancy, or hyperproliferative disorder.

In another specific embodiment, diseases and disorders involving a deficient immune responsiveness resulting in cell proliferation or in which cell proliferation is desirable for treatment, are diagnosed, or their suspected presence can be screened for, or a predisposition to develop such disorders can be detected, by detecting increased levels of the α 2M receptor 5 protein, α 2M receptor RNA, or the α 2M receptor functional activity (e.g., HSP binding or α 2M receptor antibody, *etc.*), or by detecting mutations in α 2M receptor RNA, DNA or protein (e.g., translocations in α 2M receptor nucleic acids, truncations in the gene or protein, changes in nucleotide or amino acid sequence relative to wild-type α 2M receptor) that cause increased expression or activity of the α 2M receptor. Such diseases and disorders include, 10 but are not limited to, those described in Sections 5.7, 5.8, and 5.9. By way of example, levels of the α 2M receptor protein, levels of α 2M receptor RNA, α 2M receptor binding activity, and the presence of translocations or point mutations can be determined as described above.

In a specific embodiment, levels of α 2M receptor mRNA or protein in a patient 15 sample are detected or measured, relative to the levels present in an analogous sample from a subject not having the disorder, in which increased levels indicate that the subject has, or has a predisposition to, an autoimmune disorder.

Kits for diagnostic use are also provided, that comprise in one or more containers an anti- α 2M receptor antibody, and, optionally, a labeled binding partner to the antibody. 20 Alternatively, the anti- α 2M receptor antibody can be labeled (with a detectable marker, *e.g.*, a chemiluminescent, enzymatic, fluorescent, or radioactive moiety). A kit is also provided that comprises in one or more containers a nucleic acid probe capable of hybridizing to α 2M receptor RNA. In a specific embodiment, a kit can comprise in one or more containers a pair of primers (*e.g.*, each in the size range of 6-30 nucleotides) that are capable of priming 25 amplification [*e.g.*, by polymerase chain reaction (see *e.g.*, Innis *et al.*, 1990, PCR Protocols, Academic Press, Inc., San Diego, CA), ligase chain reaction (see EP 320,308) use of Q β replicase, cyclic probe reaction, or other methods known in the art] under appropriate reaction conditions of at least a portion of an α 2M receptor nucleic acid. A kit can optionally further comprise in a container a predetermined amount of a purified α 2M receptor protein or 30 nucleic acid, *e.g.*, for use as a standard or control.

5.6 THERAPEUTIC USES

The invention further encompasses methods for modulating the immune response. The α 2M receptor recognizes and transports HSP-antigenic peptide complexes for the 35 purpose of presenting such antigenic molecules to cells of the immune system and eliciting

an immune response. Thus, the compositions and methods of the invention may be used for therapeutic treatment of HSP- α 2M receptor-related disorders and conditions, such as autoimmune diseases, cancer and infectious diseases. In particular, as described in detail hereinbelow, recombinant cells comprising HSP- α 2M receptor complexes, antibodies and other compounds that modulate the interaction between HSPs and the α 2M receptor, as well as other compounds that modulate HSP- α 2M receptor-mediated processes may be used to elicit, or block, an immune response to treat such HSP- α 2M receptor-related disorders and conditions.

10 5.6.1 THERAPEUTIC USE OF IDENTIFIED AGONISTS AND ANTAGONISTS

Compounds, such as those identified by screening methods provided herein, that modulate the interaction between HSPs and the α 2M receptor can be useful as therapeutics. Such compounds, include, but are not limited to, agonists, antagonists, such as antibodies, antisense RNAs and ribozymes. Compounds which interfere with HSP- α 2M receptor interaction can be used to block an immune response, and can be used to treat autoimmune responses and conditions. Other antibodies, agonists, antagonists, antisense RNAs and ribozymes may upregulate HSP- α 2M receptor interaction, activity, or expression, and would enhance the uptake of HSP-antigen complexes, and therefore be useful in stimulating the host's immune system prior to, or concurrent with, the administration of a vaccine.

15 20 Described below are methods and compositions for the use of such compounds in the treatment of HSP- α 2M receptor-related disorders, such as immune disorders, proliferative disorders, and infectious diseases.

In one embodiment an antagonist of HSP- α 2M receptor interaction is used to block the immune response. Such antagonists include compounds that interfere with binding of an HSP to the receptor by competing for binding to the α 2M receptor, the HSP, or the HSP- α 2M receptor complex.

25 30 In one embodiment, the antagonist is an antibody specific for the α 2M receptor, or a fragment thereof which contains the HSP ligand binding site. In another embodiment the antagonist is an antibody specific for an HSP, which interferes with binding of the HSP to the receptor.

35 In another embodiment, the antagonist is a peptide which comprises at least contiguous 10 amino acids of an HSP sequence. Such a peptide can bind to the ligand binding site of the α 2M receptor to block the interaction of an HSP or HSP complex. In another embodiment, the antagonist is a peptide which comprises at least contiguous 10 amino acids of α 2M sequence, which, like an HSP, can bind to the α 2M receptor and

interfere with the binding and uptake of HSP-antigen complexes. In yet another embodiment, the antagonist is a peptide which comprises at least contiguous 10 amino acids of α 2M receptor sequence, in particular the ECD of the α 2M receptor (or a portion thereof), which can bind to and "neutralize" natural ligands, such as HSPs, α 2M, LDL, etc.

5 Such peptides may be produced synthetically or by using standard molecular biology techniques. Amino acid sequences and nucleotide sequences of naturally occurring α 2M and HSPs are generally available in sequence databases, such as GenBank. Computer programs, such as Entrez, can be used to browse the database, and retrieve any amino acid sequence and genetic sequence data of interest by accession number. Methods for recombinant and
10 synthetic production of such peptides are described in Sections 5.1.1 and 5.1.2.

Additionally, compounds, such as those identified via techniques such as those described hereinabove, in Section 5.2, that are capable of modulating α 2M receptor gene product activity can be administered using standard techniques that are well known to those of skill in the art.

15

5.6.1.1 COMPETITIVE ANTAGONISTS OF HSP- α 2MR

In one embodiment an antagonist of HSP- α 2M receptor interaction is used to block the immune response to an HSP-antigen complex, e.g., to treat an auto-immune disorder.

Such antagonists include molecules that interfere with binding by binding to the α 2M
20 receptor (α 2MR), thereby interfering with binding of an HSP to the receptor. An example of this type of competitive inhibitor is an antibody to α 2MR, or a fragment of α 2MR which contains an HSP ligand binding site. Another example of a competitive antagonist is α 2M, or a receptor-binding fragment thereof, which itself binds to α 2M receptor, thereby blocking the binding and uptake of HSP-antigen complexes by the cell.

25 An HSP- α 2M competitive inhibitor can be any type of molecule, including but not limited to a protein, nucleic acid or drug. In a preferred embodiment, the HSP- α 2M competitive inhibitor is an α 2MR-binding or an HSP-binding peptide. Examples of such peptides are provided below.

30

5.6.1.1.1 α 2MR-BINDING PEPTIDES

α Macroglobulin peptides

In one embodiment of the present invention, an HSP- α 2MR competitive antagonist is an α macroglobulin, preferably α 2M, or α 2MR-binding portion thereof.

35

Functional expression of α 2M or α 2MR-binding portions thereof (including recombinant expression as a FX fusion protein, processing, purification and refolding) is preferably carried out as described by Holtet *et al.*, 1994, FEBS Lett. 344:242-246.

In a specific mode of the embodiment, an α 2MR-binding portion of α 2M consists of 5 or comprises a fragment of the α 2M RBD consisting of at least 10 (continuous) amino acids. In other modes of the embodiment, the fragment consists of at least 20, 30, 40, 50, 75 or 100 amino acids of the RBD. In specific modes of the embodiment, such fragments are not larger than 27, 138 or 153 amino acids. Most preferred peptides comprise one or both of amino acids Lys₁₃₇₀ and Lys₁₃₇₄. Such peptides include those consisting of amino acids 1299-1451 10 (vRBD in FIG. 7B) (SEQ ID NO:8), 1314-1451 (SEQ ID NO:9) (RBD in FIG. 7B) or 1366-1392 (SEQ ID NO:10) of the mature α 2M protein. Other preferred peptides include but are not limited to those consisting of amino acids 1300-1425 (SEQ ID NO:11), 1300-1400 (SEQ ID NO:12), 1300-1380 (SEQ ID NO:13), 1325-1425 (SEQ ID NO:14), 1325-1400 (SEQ ID NO:15), 1325-1380 (SEQ ID NO:16), 1350-1425 (SEQ ID NO:17), 1350-1400 (SEQ ID NO:18), or 1350-1380 (SEQ ID NO:19) of the mature human α 2M protein.

Derivatives or analogs of α 2M or α 2MR-binding portions of α 2M are also contemplated as competitive antagonists of HSP- α 2MR complexes. Such derivative or analogs include but are not limited to those molecules comprising regions that are substantially homologous to α 2M, the α 2M RBD or fragments thereof (e.g., in various 20 embodiments, at least 60% or 70% or 80% or 90% or 95% identity over an amino acid sequence of identical size or when compared to an aligned sequence in which the alignment is done by a computer homology program known in the art) or whose encoding nucleic acid is capable of hybridizing to a coding α 2M RBD sequence, under stringent, moderately stringent, or nonstringent conditions. In certain specific embodiments, an α 2M derivative is 25 a chimeric or fusion protein comprising an α 2M protein or α 2MR-binding portion thereof (preferably consisting of at least 10 amino acids of the α 2M RBD comprising Lys₁₃₇₀ and Lys₁₃₇₄) joined at its amino- or carboxy-terminus via a peptide bond to an amino acid sequence of a different protein.

In particular, α 2M derivatives can be made by altering α 2M coding sequences by 30 substitutions, additions or deletions that provide for functionally equivalent molecules. Due to the degeneracy of nucleotide coding sequences, other DNA sequences which encode substantially the same amino acid sequence as a α 2M gene may be used in the practice of the present invention. These include but are not limited to nucleotide sequences comprising all or α 2MR-binding portions of α 2M genes which are altered by the substitution of different 35 codons that encode a functionally equivalent amino acid residue within the sequence, thus producing a silent change. Likewise, the α 2M derivatives of the invention include, but are

not limited to, those containing, as a primary amino acid sequence, all or an α 2MR-binding portion of the amino acid sequence of an α 2M protein, including altered sequences in which functionally equivalent amino acid residues are substituted for residues within the sequence resulting in a silent change. For example, one or more amino acid residues within the 5 sequence can be substituted by another amino acid of a similar polarity which acts as a functional equivalent, resulting in a silent alteration. Substitutes for an amino acid within the sequence may be selected from other members of the class to which the amino acid belongs. For example, the nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan and methionine. The polar neutral amino acids 10 include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine. The positively charged (basic) amino acids include arginine, lysine and histidine. The negatively charged (acidic) amino acids include aspartic acid and glutamic acid.

The α 2M derivatives and analogs of the invention can be produced by various methods known in the art. The manipulations which result in their production can occur at 15 the gene or protein level. For example, the cloned α 2M gene sequence can be modified by any of numerous strategies known in the art (Maniatis, T., 1990, Molecular Cloning, A Laboratory Manual, 2d ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, New York). The sequence can be cleaved at appropriate sites with restriction endonuclease(s), followed by further enzymatic modification if desired, isolated, and ligated *in vitro*. In the production 20 of the gene encoding a derivative or analog of α 2M, care should be taken to ensure that the modified gene remains within the same translational reading frame as α 2M, uninterrupted by translational stop signals, in the gene region where the desired α 2M activity is encoded.

Manipulations of the α 2M sequence may also be made at the protein level. Included 25 within the scope of the invention are α 2M protein fragments or other derivatives or analogs which are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, 30 V8 protease, NaBH₄; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; etc.

In addition, analogs and derivatives of α 2M can be chemically synthesized. For example, an α 2MR-binding portion of α 2M can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid 35 analogs can be introduced as a substitution or addition into the α 2M sequence. Non-classical amino acids include but are not limited to the D-isomers of the common amino acids, α -

amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, γ -Abu, ϵ -Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, β -alanine, fluoro-amino acids, designer 5 amino acids such as β -methyl amino acids, C α -methyl amino acids, N α -methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

In other specific modes of the embodiment, an HSP- α 2MR competitive antagonist is another α macroglobulin or α 2MR-binding portion thereof, for example an α macroglobulin 10 RBD domain selected from Nielsen *et al.*, *supra*, Fig. 3, Group A.

RAP

In one embodiment of the present invention, an HSP- α 2MR competitive antagonist is α 2MR-associated protein (RAP) (Genbank accession no. A39875) or an α 2MR-binding 15 portion thereof. In a specific mode of the embodiment, an α 2MR-binding portion of RAP consists of or comprises a fragment of the RAP RBD consisting of at least 10 (continuous) amino acids. In other modes of the embodiment, the fragment consists of at least 20, 30, 40, 50, 75 or 100 amino acids of the RBD. In specific modes of the embodiment, such fragments are not larger than 28, 50 or 100 amino acids. In other specific modes of the embodiment, an 20 α 2MR-binding portion of RAP comprises an α 2MR-binding portion of domain 1 or 3, *e.g.* as depicted in Nielsen *et al.*, *supra*, Fig. 3, Group D or E. Expression of recombinant RAP or an α 2MR-binding portion thereof, *e.g.* domain 1 or 3, is preferably achieved as described by Andersen *et al.*, *supra*).

25 5.6.1.1.2 HSP-BINDING PEPTIDES

α 2MR peptides

In one embodiment of the present invention, an HSP- α 2MR competitive antagonist is α 2MR peptide, preferably a soluble peptide, that can bind to HSPs and therefore competitively inhibit HSP binding to the native receptor.

30 Functional expression of HSP-binding portions of α 2MR is preferably carried out as described for the CR8 domain by Huang *et al.*, 1999, *J. Biol. Chem.* 274:14130-14136. Briefly, to maintain proper folding, the protein is expressed as a GST fusion, expressed recombinantly, the GST portion cleaved, uncleaved protein removed on GSH-Sepharose, and cleaved protein refolded. Since the complement repeats bind to calcium, proper folding is 35 assayed by measuring the binding of the refolded protein to calcium.

In a specific mode of the embodiment, an HSP-binding portion of α 2MR consists of or comprises at least one complement repeat, most preferably selected from CR3-CR10. In another specific mode of the embodiment, an HSP-binding portion of α 2MR comprises a cluster of complement repeats, most preferably Cl-II. In other modes of the embodiment, the 5 HSP-binding portion consists of at least 10, more preferably at least 20, yet more preferably at least 30, yet more preferably at least 40, and most preferably at least 80 (continuous) amino acids. In specific modes of the embodiment, such fragments are not larger than 40-45 amino acids. In other specific modes of the embodiment, such fragments are not larger than 80-90 amino acids. Exemplary preferred peptides include but are not limited to those consisting of 10 amino acids 25-68 (SEQ ID NO:20), 25-110 (SEQ ID NO:21), 68-110 (SEQ ID NO:22), 853-894 (SEQ ID NO:23), 853-934 (SEQ ID NO:24), 853-974 (SEQ ID NO:25), 853-1013 (SEQ ID NO:26), 853-1060 (SEQ ID NO:27), 853-1102 (SEQ ID NO:28), 853-1183 (SEQ ID NO:29), 895-934 (SEQ ID NO:30), 895-974 (SEQ ID NO:31), 895-1013 (SEQ ID NO:32), 895-1060 (SEQ ID NO:33), 895-1102 (SEQ ID NO:34), 895-1183 (SEQ ID NO:35), 15 935-974 (SEQ ID NO:36), 935-1013 (SEQ ID NO:37), 935-1060 (SEQ ID NO:38), 935-1102 (SEQ ID NO:39), 935-1183 (SEQ ID NO:40), 975-1013 (SEQ ID NO:41), 975-1060 (SEQ ID NO:42), 975-1143 (SEQ ID NO:43), 975-1183 (SEQ ID NO:44), 1014-1060 (SEQ ID NO:45), 1014-1102 (SEQ ID NO:46), 1014-1183 (SEQ ID NO:47), 1061-1102 (SEQ ID NO:48), 1061-1143 (SEQ ID NO:49), 1061-1183 (SEQ ID NO:50), 1103-1143 (SEQ ID NO:51), 1103-1183 (SEQ ID NO:52), or 1144-1183 (SEQ ID NO:53) of human α 2MR.

Derivatives or analogs of HSP-binding portions α 2MR also contemplated as competitive antagonists of HSP- α 2MR complexes. Such derivative or analogs include but are not limited to those molecules comprising regions that are substantially homologous to the extracellular domain of α 2MR or fragments thereof (e.g., in various embodiments, at 25 least 60% or 70% or 80% or 90% or 95% identity over an amino acid sequence of identical size or when compared to an aligned sequence in which the alignment is done by a computer homology program known in the art) or whose encoding nucleic acid is capable of hybridizing to a sequence encoding an α 2MR HSP-binding sequence, under stringent, moderately stringent, or nonstringent conditions. In certain specific embodiments, an α 2MR 30 derivative is a chimeric or fusion protein comprising an HSP-binding portion of α 2MR, preferably consisting of at least one complement repeat of Cl-II) joined at its amino- or carboxy-terminus via a peptide bond to an amino acid sequence of a different protein. Such a chimeric protein can be produced recombinantly as described above, by omitting the cleavage and repurification steps.

35 Other HSP-binding α 2MR derivatives can be made by altering α 2MR coding sequences by substitutions, additions or deletions that provide for functionally equivalent

molecules. Due to the degeneracy of nucleotide coding sequences, other DNA sequences which encode substantially the same amino acid sequence as an HSP-binding α 2MR gene or gene fragment may be used in the practice of the present invention. Selection of suitable alterations and production of HSP-binding α 2MR derivatives can be made applying the same 5 principles described above for α 2M derivatives and using the general methods described in Sections 5.1.1 and 5.1.2.

HSP peptides

In another mode of the embodiment, the antagonist is an peptide which comprises at 10 least contiguous 10 amino acids of an HSP sequence. Such a peptide can bind to the ligand binding site of the α 2M receptor a block the interaction of an HSP or HSP complex.

Such peptides may be produced synthetically or by using standard molecular biology techniques. Amino acid sequences and nucleotide sequences of naturally occurring HSPs are generally available in sequence databases, such as GenBank. Computer programs, such as 15 Entrez, can be used to browse the database, and retrieve any amino acid sequence and genetic sequence data of interest by accession number. Methods for recombinant and synthetic production of such peptides are described in Sections 5.1.1 and 5.1.2.

Additionally, compounds, such as those identified via techniques such as those described hereinabove, in Section 5.2, that are capable of modulating α 2M receptor gene 20 product activity can be administered using standard techniques that are well known to those of skill in the art.

5.6.2 THERAPEUTIC USE OF THE α 2M RECEPTOR AGAINST CANCER AND INFECTIOUS DISEASES

25 In another embodiment, symptoms of certain α 2M receptor gene disorders, such as autoimmune disorders, or proliferative or differentiative disorders causing tumorigenesis or cancer, may be ameliorated by modulating the level of α 2M receptor gene expression and/or α 2M receptor gene product activity. In one embodiment, for example, a decrease in α 2M receptor gene expression may be useful to decrease α 2M receptor activity, and ameliorate the 30 symptoms of an autoimmune disorder. In this case, the level of α 2M receptor gene expression may be decreased by using α 2M receptor gene sequences in conjunction with well-known antisense, gene "knock-out," ribozyme and/or triple helix methods. In another embodiment, an increase in α 2M receptor gene expression may be desired to compensate for a mutant or impaired gene in an HSP- α 2M receptor-mediated pathway, and to ameliorate the 35 symptoms of an HSP- α 2M receptor-related disorder.

Among the compounds that may exhibit the ability to modulate the activity, expression or synthesis of the α 2M receptor gene, including the ability to ameliorate the symptoms of an HSP- α 2M receptor related disorder are antisense, ribozyme, and triple helix molecules. Such molecules may be designed to reduce or inhibit either unimpaired, or if 5 appropriate, mutant target gene activity. Techniques for the production and use of such molecules are well known to those of skill in the art.

Antisense RNA and DNA molecules act to directly block the translation of mRNA by hybridizing to targeted mRNA and preventing protein translation. Antisense approaches involve the design of oligonucleotides that are complementary to a target gene mRNA. The 10 antisense oligonucleotides will bind to the complementary target gene mRNA transcripts and prevent translation. Absolute complementarity, although preferred, is not required.

A sequence "complementary" to a portion of an RNA, as referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double-stranded antisense nucleic acids, a single strand of the 15 duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the longer the hybridizing nucleic acid, the more base mismatches with an RNA it may contain and still form a stable duplex (or triplex, as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard 20 procedures to determine the melting point of the hybridized complex.

In one embodiment, oligonucleotides complementary to non-coding regions of the α 2M receptor gene could be used in an antisense approach to inhibit translation of endogenous α 2M receptor mRNA. Antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in 25 length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

In an embodiment of the present invention, oligonucleotides complementary to the nucleic acids encoding the HSP receptor ligand binding domain are used.

Regardless of the choice of target sequence, it is preferred that in vitro studies are first 30 performed to quantitate the ability of the antisense oligonucleotide to inhibit gene expression. It is preferred that these studies utilize controls that distinguish between antisense gene inhibition and nonspecific biological effects of oligonucleotides. It is also preferred that these studies compare levels of the target RNA or protein with that of an internal control RNA or protein. Additionally, it is envisioned that results obtained using the antisense 35 oligonucleotide are compared with those obtained using a control oligonucleotide. It is preferred that the control oligonucleotide is of approximately the same length as the test

oligonucleotide and that the nucleotide sequence of the oligonucleotide differs from the antisense sequence no more than is necessary to prevent specific hybridization to the target sequence.

The oligonucleotides can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, e.g., Letsinger *et al.*, 1989, Proc. Natl. Acad. Sci. U.S.A. 86, 6553-6556; Lemaitre *et al.*, 1987, Proc. Natl. Acad. Sci. 84, 648-652; PCT Publication No. WO88/09810, published December 15, 1988) or the blood-brain barrier (see, e.g., PCT Publication No. WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents (see, e.g., Krol *et al.*, 1988, BioTechniques 6, 958-976) or intercalating agents (see, e.g., Zon, 1988, Pharm. Res. 5, 539-549). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including but not limited to 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiacytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including but not limited to arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group consisting of a phosphorothioate (S-ODNs), a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a

phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

In yet another embodiment, the antisense oligonucleotide is an α -anomeric oligonucleotide. An α -anomeric oligonucleotide forms specific double-stranded hybrids with 5 complementary RNA in which, contrary to the usual β -units, the strands run parallel to each other (Gautier *et al.*, 1987, Nucl. Acids Res. 15, 6625-6641). The oligonucleotide is a 2'-0-methylribonucleotide (Inoue *et al.*, 1987, Nucl. Acids Res. 15, 6131-6148), or a chimeric RNA-DNA analogue (Inoue *et al.*, 1987, FEBS Lett. 215, 327-330).

Oligonucleotides of the invention may be synthesized by standard methods known in 10 the art, *e.g.* by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein *et al.* (1988, Nucl. Acids Res. 16, 3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin *et al.*, 1988, Proc. Natl. Acad. Sci. U.S.A. 85, 7448-7451), etc.

15 While antisense nucleotides complementary to the target gene coding region sequence could be used, those complementary to the transcribed, untranslated region are most preferred.

In one embodiment of the present invention, gene expression downregulation is achieved because specific target mRNAs are digested by RNase H after they have hybridized 20 with the antisense phosphorothioate oligonucleotides (S-ODNs). Since no rules exist to predict which antisense S-ODNs will be more successful, the best strategy is completely empirical and consists of trying several antisense S-ODNs. Antisense phosphorothioate oligonucleotides (S-ODNs) will be designed to target specific regions of mRNAs of interest. Control S-ODNs consisting of scrambled sequences of the antisense S-ODNs will also be 25 designed to assure identical nucleotide content and minimize differences potentially attributable to nucleic acid content. All S-ODNs can be synthesized by Oligos Etc. (Wilsonville, OR). In order to test the effectiveness of the antisense molecules when applied to cells in culture, such as assays for research purposes or *ex vivo* gene therapy protocols, cells will be grown to 60-80% confluence on 100 mm tissue culture plates, rinsed with PBS 30 and overlaid with lipofection mix consisting of 8 ml Opti-MEM, 52.8 μ l Lipofectin, and a final concentration of 200 nM S-ODNs. Lipofections will be carried out using Lipofectin Reagent and Opti-MEM (Gibco BRL). Cells will be incubated in the presence of the lipofection mix for 5 hours. Following incubation the medium will be replaced with complete DMEM. Cells will be harvested at different time points post-lipofection and 35 protein levels will be analyzed by Western blot.

Antisense molecules should be targeted to cells that express the target gene, either directly to the subject *in vivo* or to cells in culture, such as in *ex vivo* gene therapy protocols. A number of methods have been developed for delivering antisense DNA or RNA to cells; e.g., antisense molecules can be injected directly into the tissue site, or modified antisense 5 molecules, designed to target the desired cells (e.g., antisense linked to peptides or antibodies that specifically bind receptors or antigens expressed on the target cell surface) can be administered systemically.

However, it is often difficult to achieve intracellular concentrations of the antisense sufficient to suppress translation of endogenous mRNAs. Therefore a preferred approach 10 utilizes a recombinant DNA construct in which the antisense oligonucleotide is placed under the control of a strong pol III or pol II promoter. The use of such a construct to transfect target cells in the patient will result in the transcription of sufficient amounts of single stranded RNAs that will form complementary base pairs with the endogenous target gene transcripts and thereby prevent translation of the target gene mRNA. For example, a vector 15 can be introduced e.g., such that it is taken up by a cell and directs the transcription of an antisense RNA. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in mammalian 20 cells. Expression of the sequence encoding the antisense RNA can be by any promoter known in the art to act in mammalian, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include but are not limited to: the SV40 early promoter region (Bernoist and Chambon, 1981, *Nature* 290, 304-310), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto *et al.*, 1980, *Cell* 25 22, 787-797), the herpes thymidine kinase promoter (Wagner *et al.*, 1981, *Proc. Natl. Acad. Sci. U.S.A.* 78, 1441-1445), the regulatory sequences of the metallothionein gene (Brinster *et al.*, 1982, *Nature* 296, 39-42), etc. Any type of plasmid, cosmid, YAC or viral vector can be used to prepare the recombinant DNA construct which can be introduced directly into the tissue site. Alternatively, viral vectors can be used that selectively infect the desired tissue, in 30 which case administration may be accomplished by another route (e.g., systemically).

Ribozyme molecules designed to catalytically cleave target gene mRNA transcripts can also be used to prevent translation of target gene mRNA and, therefore, expression of target gene product. (See, e.g., PCT International Publication WO90/11364, published October 4, 1990; Sarver *et al.*, 1990, *Science* 247, 1222-1225). In an embodiment of the 35 present invention, oligonucleotides which hybridize to the HSP receptor gene are designed to be complementary to the nucleic acids encoding the HSP receptor ligand binding domain.

Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. (For a review, see Rossi, 1994, *Current Biology* 4, 469-471). The mechanism of ribozyme action involves sequence specific hybridization of the ribozyme molecule to complementary target RNA, followed by an endonucleolytic cleavage event. The 5 composition of ribozyme molecules must include one or more sequences complementary to the target gene mRNA, and must include the well known catalytic sequence responsible for mRNA cleavage. For this sequence, see, *e.g.*, U.S. Patent No. 5,093,246, which is incorporated herein by reference in its entirety.

While ribozymes that cleave mRNA at site specific recognition sequences can be 10 used to destroy target gene mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and 15 production of hammerhead ribozymes is well known in the art and is described more fully in Myers, 1995, *Molecular Biology and Biotechnology: A Comprehensive Desk Reference*, VCH Publishers, New York, (see especially fig. 4, p. 833) and in Haseloff & Gerlach, 1988, *Nature*, 334, 585-591, which is incorporated herein by reference in its entirety.

Preferably the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the target gene mRNA, *i.e.*, to increase efficiency and minimize the 20 intracellular accumulation of non-functional mRNA transcripts.

The ribozymes of the present invention also include RNA endoribonucleases 25 (hereinafter "Cech-type ribozymes") such as the one that occurs naturally in *Tetrahymena thermophila* (known as the IVS, or L-19 IVS RNA) and that has been extensively described by Thomas Cech and collaborators (Zaug *et al.*, 1984, *Science*, 224, 574-578; Zaug and Cech, 1986, *Science*, 231, 470-475; Zaug *et al.*, 1986, *Nature*, 324, 429-433; published International patent application No. WO 88/04300 by University Patents Inc.; Been & Cech, 1986, *Cell*, 47, 207-216). The Cech-type ribozymes have an eight base pair active site which hybridizes to a target RNA sequence whereafter cleavage of the target RNA takes place. The invention encompasses those Cech-type ribozymes which target eight base-pair active site 30 sequences that are present in the target gene.

As in the antisense approach, the ribozymes can be composed of modified oligonucleotides (*e.g.*, for improved stability, targeting, etc.) and should be delivered to cells that express the target gene *in vivo*. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive pol III or pol II 35 promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous target gene messages and inhibit translation. Because ribozymes unlike

antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

Endogenous target gene expression can also be reduced by inactivating or "knocking out" the target gene or its promoter using targeted homologous recombination (e.g., see 5 Smithies *et al.*, 1985, *Nature* 317, 230-234; Thomas & Capecchi, 1987, *Cell* 51, 503-512; Thompson *et al.*, 1989, *Cell* 5, 313-321; each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional target gene (or a completely unrelated 10 DNA sequence) flanked by DNA homologous to the endogenous target gene (either the coding regions or regulatory regions of the target gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express the target gene *in vivo*. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the target gene. Such approaches are particularly suited modifications to ES (embryonic stem) cells can be used to generate animal offspring with an inactive target gene (e.g., see Thomas & Capecchi, 1987 and Thompson, 1989, *supra*). However this 15 approach can be adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors.

Alternatively, endogenous target gene expression can be reduced by targeting deoxyribonucleotide sequences complementary to the regulatory region of the target gene (i.e., the target gene promoter and/or enhancers) to form triple helical structures that prevent 20 transcription of the target gene in target cells in the body. (See generally, Helene, 1991, *Anticancer Drug Des.*, 6(6), 569-584; Helene *et al.*, 1992, *Ann. N.Y. Acad. Sci.*, 660, 27-36; and Maher, 1992, *Bioassays* 14(12), 807-815).

Nucleic acid molecules to be used in triple helix formation for the inhibition of transcription should be single stranded and composed of deoxyribonucleotides. The base 25 composition of these oligonucleotides must be designed to promote triple helix formation via Hoogsteen base pairing rules, which generally require sizeable stretches of either purines or pyrimidines to be present on one strand of a duplex. Nucleotide sequences may be pyrimidine-based, which will result in TAT and CGC⁺ triplets across the three associated strands of the resulting triple helix. The pyrimidine-rich molecules provide base 30 complementarity to a purine-rich region of a single strand of the duplex in a parallel orientation to that strand. In addition, nucleic acid molecules may be chosen that are purine-rich, for example, contain a stretch of G residues. These molecules will form a triple helix with a DNA duplex that is rich in GC pairs, in which the majority of the purine residues are located on a single strand of the targeted duplex, resulting in GGC triplets across the three 35 strands in the triplex.

Alternatively, the potential sequences that can be targeted for triple helix formation may be increased by creating a so called "switchback" nucleic acid molecule. Switchback molecules are synthesized in an alternating 5'-3', 3'-5' manner, such that they base pair with first one strand of a duplex and then the other, eliminating the necessity for a sizeable stretch 5 of either purines or pyrimidines to be present on one strand of a duplex.

In instances wherein the antisense, ribozyme, and/or triple helix molecules described herein are utilized to inhibit mutant gene expression, it is possible that the technique may so efficiently reduce or inhibit the transcription (triple helix) and/or translation (antisense, ribozyme) of mRNA produced by normal target gene alleles that the possibility may arise 10 wherein the concentration of normal target gene product present may be lower than is necessary for a normal phenotype. In such cases, to ensure that substantially normal levels of target gene activity are maintained, therefore, nucleic acid molecules that encode and express target gene polypeptides exhibiting normal target gene activity may, be introduced into cells via gene therapy methods such as those described, below, in Section 5.6.3 that do not contain 15 sequences susceptible to whatever antisense, ribozyme, or triple helix treatments are being utilized. Alternatively, in instances whereby the target gene encodes an extracellular protein, it may be preferable to co-administer normal target gene protein in order to maintain the requisite level of target gene activity.

Anti-sense RNA and DNA, ribozyme, and triple helix molecules of the invention may 20 be prepared by any method known in the art for the synthesis of DNA and RNA molecules, as discussed above. These include techniques for chemically synthesizing oligodeoxyribonucleotides and oligoribonucleotides well known in the art such as for example solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by *in vitro* and *in vivo* transcription of DNA sequences encoding the antisense RNA molecule. 25 Such DNA sequences may be incorporated into a wide variety of vectors that incorporate suitable RNA polymerase promoters such as the T7 or SP6 polymerase promoters. Alternatively, antisense cDNA constructs that synthesize antisense RNA constitutively or inducibly, depending on the promoter used, can be introduced stably into cell lines.

30 5.6.3 GENE REPLACEMENT THERAPY

With respect to an increase in the level of normal α 2M receptor gene expression and/or α 2M receptor gene product activity, α 2M receptor gene nucleic acid sequences can, for example, be utilized for the treatment of immune disorders resulting in proliferative disorders such as cancer. Such treatment can be administered, for example, in the form of 35 gene replacement therapy. Specifically, one or more copies of a normal α 2M receptor gene or a portion of the α 2M receptor gene that directs the production of an α 2M receptor gene

product exhibiting normal α 2M receptor gene function, may be inserted into the appropriate cells within a patient, using vectors that include, but are not limited to adenovirus, adeno-associated virus, and retrovirus vectors, in addition to other particles that introduce DNA into cells, such as liposomes.

5 Gene replacement therapy techniques should be capable of delivering α 2M receptor gene sequences to cell types that express the HSP receptor within patients. Thus, in one embodiment, techniques that are well known to those of skill in the art (see, e.g., PCT Publication No. WO89/10134, published April 25, 1988) can be used to enable α 2M receptor gene sequences to be delivered to developing cells of the myeloid lineage, for example, to the
10 bone marrow. In another specific embodiment, gene replacement can be accomplished using macrophages *in vitro*, and delivered to a patient using the techniques of adoptive immunotherapy.

In another embodiment, techniques for delivery involve direct administration of such α 2M receptor gene sequences to the site of the cells in which the α 2M receptor gene sequences are to be expressed, e.g., directly at the site of the tumor.

15 Additional methods that may be utilized to increase the overall level of α 2M receptor gene expression and/or α 2M receptor gene product activity include the introduction of appropriate α 2M receptor-expressing cells, preferably autologous cells, into a patient at positions and in numbers that are sufficient to ameliorate the symptoms of an α 2M receptor disorder. Such cells may be either recombinant or non-recombinant.

20 Among the cells that can be administered to increase the overall level of α 2M receptor gene expression in a patient are cells that normally express the α 2M receptor gene.

25 Alternatively, cells, preferably autologous cells, can be engineered to express α 2M receptor gene sequences, and may then be introduced into a patient in positions appropriate for the amelioration of the symptoms of an α 2M receptor disorder or a proliferative or viral disease, e.g., cancer and tumorigenesis. Alternately, cells that express an unimpaired α 2M receptor gene and that are from a MHC matched individual can be utilized, and may include, for example, brain cells. The expression of the α 2M receptor gene sequences is controlled by the appropriate gene regulatory sequences to allow such expression in the necessary cell types. Such gene regulatory sequences are well known to the skilled artisan. Such cell-based gene therapy techniques are well known to those skilled in the art, see, e.g., Anderson, U.S. Patent No. 5,399,349.

30 When the cells to be administered are non-autologous cells, they can be administered using well known techniques that prevent a host immune response against the introduced cells from developing. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular

environment, does not allow the introduced cells to be recognized by the host immune system.

5.6.4 DELIVERY OF SOLUBLE α 2M RECEPTOR POLYPEPTIDES

5 Genetically engineered cells that express soluble α 2M receptor ECDs or fusion proteins, *e.g.*, fusion Ig molecules can be administered *in vivo* where they may function as "bioreactors" that deliver a supply of the soluble molecules. Such soluble α 2M receptor polypeptides and fusion proteins, when expressed at appropriate concentrations, should neutralize or "mop up" HSPs or other native ligand for the α 2M receptor, and thus act as 10 inhibitors of α 2M receptor activity and may therefore be used to treat HSP- α 2M receptor-related disorders and diseases, such as autoimmune disorders, proliferative disorders, and infectious diseases.

5.6.5 DELIVERY OF DOMINANT NEGATIVE MUTANTS

15 In another embodiment of the invention, dominant negative mutants ("dominant negatives") may be used therapeutically to block the immune response to an HSP-antigen complex, *e.g.*, to treat an auto-immune disorder. In general, such dominant-negatives are mutants which, when expressed, interact with ligand (*i.e.*, HSP-antigenic molecule complex), but lack one or more functions, *i.e.* endocytotic functions and/or signaling 20 functions, of normal α 2MR. Such mutants interfere with the function of normal α 2MR in the same cell or in a different cell, *e.g.* by titration of HSP-peptide complexes from the wild type receptor. Such a mutation, for example, can be one or more point mutation(s), a deletion, insertion, or other mutation in either the extracellular of the 515 kDa subunit, or the 25 extracellular, transmembrane or intracellular domains of the 85 kDa subunit of the alpha(2) macroglobulin receptor (*see* Krieger and Herz, 1994, Annu. Rev. Biochem 63:601-637 for α 2MR subunit configuration). However, in construction of dominant negative mutations in the either subunit, care should be taken to ensure that the cleavage domain (signaling 30 cleavage between aas 3525 and 3526 of the precursor of α 2MR) remains intact so that the 515 kDa subunit is processed and presented on the cell surface. Additionally, care should be taken to ensure that the domains by which the two subunits associate should also remain 35 functional. For example, in a specific embodiment, the C-terminal intracellular domain of the 85 kDa subunit is truncated. In another embodiment, a point mutation on the N-terminal 515 kDa subunit blocks endocytosis but not ligand binding. In another embodiment, the N-terminal 515 kDa subunit is expressed as a fusion protein, wherein the C-terminus of said

fusion protein is the transmembrane domain and optionally the intracellular domain, of another Type I single transmembrane receptor.

5 Expression of a such a dominant negative mutation in cell can block uptake of ligand by normal functional receptors in the same or neighboring cells by titrating out the amount of available ligand. Thus, a recombinant antigen presenting cell expressing such a dominant negative can be used to titrate out HSP-antigenic molecule complexes when administered to a patient in need of treatment for an autoimmune disorder.

5.7 TARGET AUTOIMMUNE DISEASES

10 Autoimmune diseases that can be treated by the methods of the present invention include, but are not limited to, insulin dependent diabetes mellitus (*i.e.*, IDDM, or autoimmune diabetes), multiple sclerosis, systemic lupus erythematosus, Sjogren's syndrome, scleroderma, polymyositis, chronic active hepatitis, mixed connective tissue disease, primary biliary cirrhosis, pernicious anemia, autoimmune thyroiditis, idiopathic Addison's disease, 15 vitiligo, gluten-sensitive enteropathy, Graves' disease, myasthenia gravis, autoimmune neutropenia, idiopathic thrombocytopenia purpura, rheumatoid arthritis, cirrhosis, pemphigus vulgaris, autoimmune infertility, Goodpasture's disease, bullous pemphigoid, discoid lupus, ulcerative colitis, and dense deposit disease. The diseases set forth above, as referred to herein, include those exhibited by animal models for such diseases, such as, for example non- 20 obese diabetic (NOD) mice for IDDM and experimental autoimmune encephalomyelitis (EAE) mice for multiple sclerosis.

25 The methods of the present invention can be used to treat such autoimmune diseases by reducing or eliminating the immune response to the patient's own (self) tissue, or, alternatively, by reducing or eliminating a pre-existing autoimmune response directed at tissues or organs transplanted to replace self tissues or organs damaged by the autoimmune response.

5.8 TARGET INFECTIOUS DISEASES

30 The infectious diseases that can be treated or prevented using the methods and compositions of the present invention include those caused by intracellular pathogens such as viruses, bacteria, protozoans, and intracellular parasites. Viruses include, but are not limited to viral diseases such as those caused by hepatitis type B virus, parvoviruses, such as adeno-associated virus and cytomegalovirus, papovaviruses such as papilloma virus, 35 polyoma viruses, and SV40, adenoviruses, herpes viruses such as herpes simplex type I (HSV-I), herpes simplex type II (HSV-II), and Epstein-Barr virus, poxviruses, such as variola

(smallpox) and vaccinia virus, RNA viruses, including but not limited to human immunodeficiency virus type I (HIV-I), human immunodeficiency virus type II (HIV-II), human T-cell lymphotropic virus type I (HTLV-I), and human T-cell lymphotropic virus type II (HTLV-II); influenza virus, measles virus, rabies virus, Sendai virus, picornaviruses such as poliomyelitis virus, coxsackieviruses, rhinoviruses, reoviruses, togaviruses such as rubella virus (German measles) and Semliki forest virus, arboviruses, and hepatitis type A virus.

5 In another embodiment, bacterial infections can be treated or prevented such as, but not limited to disorders caused by pathogenic bacteria including, but not limited to, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Neisseria gonorrhoea*, *Neisseria meningitidis*, *Corynebacterium diphtheriae*, *Clostridium botulinum*, *Clostridium perfringens*, *Clostridium tetani*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella ozaenae*, *Klebsiella rhinoscleromotis*, *Staphylococcus aureus*, *Vibrio cholerae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Campylobacter* (*Vibrio*) *fetus*, *Campylobacter jejuni*, *Aeromonas hydrophila*, *Bacillus cereus*, *Edwardsiella tarda*, *Yersinia enterocolitica*, *Yersinia pestis*, *Yersinia pseudotuberculosis*, *Shigella dysenteriae*, *Shigella flexneri*, *Shigella sonnei*, *Salmonella typhiimurium*, *Salmonella typhi*, *Treponema pallidum*, *Treponema pertenue*, *Treponema carateum*, *Borrelia vincentii*, *Borrelia burgdorferi*, *Leptospira icterohemorrhagiae*, *Mycobacterium tuberculosis*, *Toxoplasma gondii*, *Pneumocystis carinii*, *Francisella tularensis*, *Brucella abortus*, *Brucella suis*, *Brucella melitensis*, *Mycoplasma spp.*, *Rickettsia prowazekii*, *Rickettsia tsutsugumushi*, *Chlamydia spp.*, and *Helicobacter pylori*.

In another preferred embodiment, the methods can be used to treat or prevent infections caused by pathogenic protozoans such as, but not limited to, *Entamoeba histolytica*, *Trichomonas tenas*, *Trichomonas hominis*, *Trichomonas vaginalis*, *Trypanosoma gambiense*, *Trypanosoma rhodesiense*, *Trypanosoma cruzi*, *Leishmania donovani*, *Leishmania tropica*, *Leishmania braziliensis*, *Pneumocystis pneumonia*, *Plasmodium vivax*, *Plasmodium falciparum*, and *Plasmodium malaria*.

5.9 TARGET PROLIFERATIVE CELL DISORDERS

30 With respect to specific proliferative and oncogenic disease associated with HSP- α 2M receptor activity, the diseases that can be treated or prevented by the methods of the present invention include, but are not limited to: human sarcomas and carcinomas, *e.g.*, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, *35* synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon

carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma,
5 choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendrogioma, meningioma, melanoma, neuroblastoma, retinoblastoma; leukemias, *e.g.*, acute lymphocytic leukemia and acute
10 myelocytic leukemia (myeloblastic, promyelocytic, myelomonocytic, monocytic and erythroleukemia); chronic leukemia (chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia); and polycythemia vera, lymphoma (Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenström's macroglobulinemia, and heavy chain disease.

15 Diseases and disorders involving a deficiency in cell proliferation or in which cell proliferation is desired for treatment or prevention, and that can be treated or prevented by inhibiting the α 2M receptor function, include but are not limited to degenerative disorders, growth deficiencies, hypoproliferative disorders, physical trauma, lesions, and wounds; for example, to promote wound healing, or to promote regeneration in degenerated, lesioned or
20 injured tissues, etc.

5.10 PHARMACEUTICAL PREPARATIONS AND METHODS OF ADMINISTRATION

The compounds that are determined to affect α 2M receptor gene expression or gene
25 product activity can be administered to a patient at therapeutically effective doses to treat or ameliorate a cell proliferative disorder. A therapeutically effective dose refers to that amount of the compound sufficient to result in amelioration of symptoms of such a disorder.

5.10.1 EFFECTIVE DOSE

30 Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD₅₀/ED₅₀. Compounds that exhibit
35 large therapeutic indices are preferred. While compounds that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such compounds to the

site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies 5 preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma 10 concentration range that includes the IC₅₀ (*i.e.*, the concentration of the test compound that achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

15 5.10.2 FORMULATIONS AND USE

Pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more physiologically acceptable carriers or excipients.

Thus, the compounds and their physiologically acceptable salts and solvates may be 20 formulated for administration by inhalation or insufflation (either through the mouth or the nose) or oral, buccal, parenteral or rectal administration.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.*, pregelatinised maize starch, 25 polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (*e.g.*, lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (*e.g.*, magnesium stearate, talc or silica); disintegrants (*e.g.*, potato starch or sodium starch glycolate); or wetting agents (*e.g.*, sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for 30 example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (*e.g.*, sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (*e.g.*, lecithin or acacia); non-aqueous vehicles (*e.g.*, almond oil, oily 35 esters, ethyl alcohol or fractionated vegetable oils); and preservatives (*e.g.*, methyl or propyl-

p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavoring, coloring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

5 For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, *e.g.*,

10 dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of *e.g.*, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

15 The compounds may be formulated for parenteral administration by injection, *e.g.*, by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for 20 constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

25 In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange 30 resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The compositions may, if desired, be presented in a pack or dispenser device that may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration.

6. EXAMPLE: IDENTIFICATION OF α 2M RECEPTOR AS AN HSP RECEPTOR

6.1 INTRODUCTION

The Example presented herein describes the successful identification of an interaction between gp96 and the α 2M receptor present in macrophages and dendritic cells. The 5 experiments presented herein form the basis for isolating α 2M receptor polypeptides and for the screening, diagnostic, and therapeutic methods of the present invention.

The Applicant of the present invention noted that certain observations were inconsistent with a "direct transfer" model of HSP-chaperoned peptide antigen presentation. First, the immunogenicity of HSP preparations is dependent on the presence of functional 10 phagocytic cells but not B cells or other nonprofessional antigen-presenting cells, (Udono and Srivastava, 1993, *supra*; Suto and Srivastava, 1995, *supra*), whereas free peptides can sensitize all cell types. Second, extremely small quantities of HSP-peptide complexes were effective in eliciting specific immunity, *i.e.*, gp96-chaperoned peptides are several hundred times as effective as free peptides in sensitizing macrophages for CTL recognition, 15 suggesting the possibility of a specific uptake mechanism. Third, gp96-chaperoned peptides elicited an MHC I response that was not limited by the size of peptide. Finally, the processing of gp96-peptide complexes in macrophage was found to be sensitive to Brefeldin A (BFA), which blocks transport through the Golgi apparatus, suggesting that processing occurred through an intercellular mechanism. These observations led to the hypothesis that 20 HSP-chaperoned peptides may be processed internally and re-presented by MHC class I molecules on the cell surfaces of macrophages (Suto and Srivastava, 1995, *supra*). There is also the hypothesis that the mannose receptor is used in the uptake of gp96 but no mechanism has been proposed for the non-glycosylated HSPs, such as HSP70 (Ciupitu *et al.*, 1998, *J. Exp. Med.*, 187: 685-691). Others suggested that a novel intracellular trafficking pathway 25 may be involved for the transport of peptides from the extracellular medium into the lumen of ER) Day *et al.*, 1997, *Proc. Natl. Acad. Sci.* 94:8065-8069; Nicchitta, 1998, *Curr. Opin. in Immunol.* 10:103-109). Further suggestions include the involvement of phagocytes which (a) possess an ill-defined pathway to shunt protein from the phagosome into the cytosol where it 30 would enter the normal class I pathway; (b) digest ingested material in lysosomes and regurgitate peptides for loading on the surface to class I molecules (Bevan, 1995, *J. Exp. Med.* 192:639-41). The discovery of a receptor for heat shock protein as disclosed herein helps to resolve the paradox of how extracellular antigenic peptides complexed to HSPs can be presented by MHC class I molecules on antigen presenting cells.

6.2 MATERIALS AND METHODS

Affinity chromatography. Proteins (1mg) in 2ml volume were incubated with 2ml of equilibrated AminoLink beads in PBS with a reductant (NaCNBH₃) for 1 hour. Uncoupled protein was removed by extensive washing of the column and unreactive groups quenched.

5 Immobilization yields were typically >92% of the starting amount of protein. Columns were stored at 4°C until used. Such columns were made with gp96 (purified as described in Srivastava *et al.*, 1986, Proc. Natl. Acad. Sci., U.S.A. 83:3407-3411) and albumin. For membrane purification, cells were lysed by dounce homogenization in hypotonic buffer containing PMSF. Unlyzed cells and nuclei were removed by centrifugation at 1000g for 5

10 mm. The postnuclear supematant was centrifuged at 100,000g for 90 mins. The pellet contains total membranes and was fractionated by aqueous two-phase partition with a dextran/polyethylene glycol biphasic. Briefly membranes were resuspended in PEG (33% wt/wt in 0.22 M sodium phosphate buffer, pH 6.5) and underlaid gently with dextran (20%wt/wt in 0.22M sodium phosphate buffer, pH 6.5). The two phases were mixed gently

15 and centrifuged at 2000 g for 15 mins. The white material at the interphase was enriched for plasma membranes, whose proteins were extracted by 2 hr incubation in 20mM Tris buffer (pH8, containing 0.08% octylglucoside) at 4°C.

Photo cross-linking of gp96 to putative receptor. The cross-linker (SASP, (Pierce) was labeled with I¹²⁵ using iodobeads (Pierce). Radiolabeled SASP was covalently attached

20 to gp96 by incubation at room temperature for 1 hr. Free SASP and I¹²⁵ were removed by size exclusion column (KwikSep columns, Pierce). For cross-linking studies, I¹²⁵-SASP-gp96 (50 µg gp96) was incubated with purified CD11b⁺ cells. Unbound protein was removed by washing. All procedures to this point were carried out in very dim light. Proteins were cross-linked with UV light. Cells were lysed with lysis buffer (0.5%NP40, 10mM Tris,

25 1mMEDTA, 150mM NaCl) and treated with 100 mM 2-mercaptoethanol to cleave the cross-linker. *Cell lysates were analyzed by SDS-PAGE and autoradiography.*

Re-presentation assays. Re-presentation assays were carried out as described (Suto and Srivastava, 1995, Science 269:1585-1588). Antigen presenting cells (RAW264.7 macrophage cell line) were plated at a 1:1 ratio with AH1 -specific T cells in complete

30 RPMI. Approximately 10,000 cells of each type were used. Gp96 (10 µg/ml) chaperoning the AH1-20 mer peptide (RVTYHSPSYVYHQFERRAK) was added to the cells and the entire culture was incubated for 20 hrs. Stimulation of T cells was measured by quantifying the amount of IFN-γ released into the supernatants by ELISA (Endogen).

Protein Microsequencing. Proteins identified by affinity chromatography were

35 analyzed on SDS-PAGE and stained with coomasie blue or transferred onto PVDF membrane and stained with coomasie blue, all of it under keratin-free conditions. Protein

bands were excised with a razor from the gel or membrane. Tryptic peptides from an 80kDa faint coomassie band were extracted by 50% acetonitrile, 5% formic acid, dried, and loaded onto a 75 m 10 cm, reverse-phase C18, microcapillary column (3 μ l vol) and tryptic peptides were separated by on-line microcapillary liquid chromatography-tendem mass spectrometry followed by database searching using the SEQUEST program as previously described. (Gatlin *et al.*, 2000, *Anal. Chem.* 72:757-63; Link *et al.*, 1999, *Nat. Biotechnol.* 17:676-82). The analysis was carried out in a data-dependent auto-MS/MS fashion using a Finnigan LCQ iontrap Mass Spectrometer.

10 6.3 RESULTS

Identification of an 80 kDa protein as a potential gp96 receptor. Homogenous preparations of gp96 were coupled to FITC and the gp96-FITC was used to stain RAW264.7 cells, shown to be functionally capable of re-presenting gp96-chaperoned peptides. Gp96-FITC but not control albumin-FITC preparations stained the cell surface of RAW264.7 cells (FIG. 1A). Plasma membrane preparations of cell surface-biotinylated RAW264.7 cells were solubilized in 0.08% octyl-glucoside and the soluble extract was applied to a gp96-Sepharose column. The bound proteins were eluted with 3M sodium chloride. SDS-PAGE analysis of the eluate showed 2 major bands of ~75-80 kDa size (FIG. 1B, top left). Blotting of this gel with avidin-peroxidase showed that both bands were biotinylated, indicating their surface localization (FIG. 1B, bottom left). Affinity purification of membrane extracts of RAW264.7 cells over control serum albumin affinity columns did not result in isolation of any proteins, nor did probing of immunoblots of such gels with avidin peroxidase detect any albumin-binding surface proteins (FIG. 1B, top and bottom center lanes). As an additional control, chromatography of membrane extracts of P815 cells which do not bind gp96-FITC and which do not re-present gp96-chaperoned peptides, on gp96 affinity columns did not result in elution of any gp96-binding proteins (FIG. 1B, top and bottom right lanes).

In parallel experiments, gp96 molecules were coupled to the radio-iodinated linker sulfosuccinimidyl (4-azidosalicylamido) hexanoate (SASD) which contains a photo cross-linkable group. Gp96-SASD-I¹²⁵ was pulsed onto peritoneal macrophages, which have been shown previously to re-present gp96-chaperoned peptides (Suto and Srivastava, 1995, *Science* 269:1585-1588). Excess gp96-SASD was removed by multiple rounds of washing of the cells and photoactivation was carried out by exposure of cells to UV light for 10 min. Cell lysates were reduced in order to transfer the I¹²⁵ group to the putative gp96 ligand and were analyzed by SDS- PAGE followed by autoradiography. The gp96 molecule was observed to cross-link to an ~80 kDa band specifically present in re-presentation-competent macrophage but not in the re-presentation-incompetent P815 cells (FIG. 1C). This band

appears to correspond in size to the larger of the two bands seen in eluates of gp96 affinity columns (FIG. 1D). No band corresponding to the lower band in that preparation is seen in the photo cross-linked preparation. The observation of a specific binding of gp96 to an 80 kDa protein in two different re-presentation-competent cell types, but not in a re-presentation-incompetent cell line, and by two independent assays supported the candidacy of the 80 kDa molecule for the gp96 receptor.

5 *Antiserum against the 80 kDa protein inhibits re-presentation of a gp96-chaperoned antigenic peptide.* The eluates containing the 75-80 kDa proteins were used to immunize a New Zealand white rabbit, and pre-immune and immune sera were used to probe blots of 10 plasma membrane extracts of the re-presentation-competent RAW264.7 and primary peritoneal macrophages and the re-presentation-incompetent P815 cells. The immune but not the pre-immune serum detected the 80 kDa band (and a faint lower 75 kDa band) in plasma membrane extracts of primary macrophage and the RAW264.7 membranes but not of P815 cells (FIG. 2A). The pre-immune and immune sera were tested in a functional assay for their 15 ability to block re-presentation of gp96-chaperoned peptides. The L^d-restricted epitope AH1 derived from the gp70 antigen of murine colon carcinoma CT26 (Huang *et al.*, 1996, Proc. Natl. Acad. Sci. U.S.A. 93:9730-9735) was used as the model system. Complexes of gp96 with an AH1 precursor (used to inhibit direct presentation) were pulsed onto RAW264.7 cells which were used to stimulate a L^d/AH1-specific CD8+ T cell clone. Release of interferon- γ 20 by the clones was measured as a marker of their activation. RAW264.7 cells were able to re-present gp96-chaperoned AH1 precursor effectively in this assay. It was observed that at the highest concentration, the immune sera inhibited re-presentation completely (FIG. 2B). Although the pre-immune serum was ineffective in inhibiting representation as compared to the immune sera, it did inhibit re-presentation significantly at higher concentrations. The 25 significance of this observation became clear later when we determined the identity of the gp96 receptor. Repeated immunizations with the affinity-purified gp96-binding proteins did not result in corresponding increase in antibody titers.

30 *Identification of the 80 kDa protein as an amino terminal fragment of the heavy chain of the α 2M receptor.* The 80 kDa protein eluted from the gp96 affinity column was resolved on SDS-PAGE and visualized by staining with Coomassie Brilliant Blue. The protein band was subjected to in-gel trypsin digestion and mass spectrometry-based protein microsequencing as described in the methods in Section 6.2. Four independent tryptic peptides corresponding to N-terminal region of the α 2-macroglobulin (α 2M) receptor, designated by immunologists as CD91, were identified (FIG. 3C).

35 *α 2M inhibits re-presentation of a gp96-chaperoned antigenic peptide by RAW264.7.* α 2M receptor is one of the known natural ligands for the α 2M receptor. Its ability to inhibit

re-presentation of gp96-chaperoned antigenic peptide AH1 was tested in the assay described in FIG. 2. α 2M but not control proteins selectin (CD62) or serum albumin was observed to inhibit re-presentation completely and titratably (FIG. 4). This observation was also consistent with the result in FIG. 2 that while the pre-immune serum did not detect an 80 kDa band in plasma membranes of RAW264.7 cells, it did inhibit re-presentation to some degree at high concentrations. Thus, by structural as well as functional criteria, the α 2M receptor was determined to fulfill the criteria essential for a receptor for gp96.

6.4 DISCUSSION

The α 2M receptor, which is also designated CD91, was initially identified as a protein related to the low density lipoprotein (LDL) receptor Related Protein (LRP) (Strickland *et al.*, 1990, *J. Biol. Chem.* 265:17401-17404; Kristensen *et al.*, 1990, *FEBS Lett.* 276:151-155). The protein consists of an ~420 kDa α subunit, an 85 kDa β subunit and a 39 kDa tightly associated molecule (RAP). The α and β subunits are encoded by a single transcript of ~15 Kb in size (Van Leuven *et al.*, 1993, *Biochim. Biophys. Acta.* 1173:71-74). The receptor has been shown to be present in cells of the monocytic lineage and in hepatocytes, fibroblasts and keratinocytes. CD91 has been shown previously to bind the activated form of the plasma glycoprotein α 2M, which binds to and inhibits a wide variety of endoproteinases. α 2M receptor also binds to other ligands such as transforming growth factor β (O'Connor-McCourt *et al.*, 1987, *J. Biol. Chem.* 262:14090-14099), platelet-derived growth factor (Huang *et al.*, 1984, *Proc. Natl. Acad. Sci. U.S.A.* 81:342-346), and fibroblast growth factor (Dennis *et al.*, 1989, *J. Biol. Chem.* 264:7210-7216). α 2M is thus believed to regulate, and specifically diminish, the activities of its various ligands. Complexed with these various ligands, α 2M binds α 2M receptor on the cell surface and is internalized through receptor-mediated endocytosis. Uptake of α 2M-complexed ligands has been assumed thus far to be the primary function of the α 2M receptor, although a role for it in lipid metabolism is also assumed. α 2M receptor ligands other than α 2M, such as tissue-specific plasminogen activator-inhibitor complex (Orth *et al.*, 1992, *Proc. Natl. Acad. Sci. U.S.A.* 89:7422-7426) and urokinase-PAI1 complex (Nykjaer *et al.*, 1992, *J. Biol. Chem.* 267:14543-14546), have been identified. These ligands attest to a role for α 2M receptor in clearing a range of extracellular, plasma products.

The studies reported here show that the heat shock protein gp96 is an additional ligand for the α 2M receptor. The human gp96-coding gene has been mapped previously by us at chromosome 12 (q24.2→q24.3) (Maki *et al.*, 1993, *Somatic Cell Mol. Gen.* 19:73-81). It is of interest in this regard that the α 2M receptor gene has been mapped to the same chromosome and at a not too distant location (q13→q14) (Hilliker *et al.* *Genomics* 13:472-

474). Gp96 binds α 2M receptor directly and not through other ligands such as α 2M. Homogenous preparations of gp96, in solution, or cross-linked to a solid matrix, bind to the α 2M receptor. Indeed, the major ligand for the α 2M receptor, α 2M, actually inhibits interaction of gp96 with α 2M receptor, instead of promoting it, providing evidence that gp96 is a direct ligand for the α 2M receptor. The 80 kDa protein shown to bind gp96 is clearly an amino terminal degradation product of the α subunit of the α 2M receptor. Degradation products of the α 2M receptor in this size range have also been observed in previous studies (Jensen *et al.*, 1989, *Biochem. Arch.* 5:171-176), and may indicate the existence of a discrete ectodomain in the α 2M receptor which may be particularly sensitive to proteolytic cleavage.

10 As shown here, the gp96- α 2M receptor interaction provides a new type of function for α 2M receptor, a function of a sensor, not only of the extracellular environment with its previously known plasma-based ligands, but also a sensor of the intracellular milieu as well. HSPs such as gp96 are obligate intracellular molecules and are released into the extracellular milieu only under conditions of necrotic (but not apoptotic) cell death. Thus, the α 2M
15 receptor may act as a sensor for necrotic cell death (see FIG. 5), just as the scavenger receptor CD36 and the recently identified phosphatidyl serine-binding protein act as sensors of apoptotic cell death and receptors for apoptotic cells (Savill *et al.*, 1992, *J. Clin. Invest.* 90:1513-1522; Fadok *et al.*, 2000, *Nature* 405:85-90). Interaction of the macrophages with the apoptotic cells leads to a down-regulation of the inflammatory cytokines such as
20 TNF (Fadok *et al.*, 2000, *supra*), while gp96-APC interaction leads to re-presentation of gp96-chaperoned peptides by MHC I molecules of the APC, followed by stimulation of antigen-specific T cells (Suto and Srivastava, 1995, *supra*) and, in addition, secretion of pro-inflammatory cytokines such as TNF, GM-CSF and IL-12. Interestingly, α 2M, an independent ligand for the α 2M receptor, inhibits representation of gp96-chaperoned
25 peptides by macrophages. This observation suggests that re-presentation of gp96-chaperoned peptides can not occur physiologically in blood, but only within tissues as a result of localized necrotic cell death. This is consistent with the complete absence of gp96 or other HSPs in blood under all conditions tested. Together, these observations point towards a possible mechanism whereby the release of HSPs in the blood as a result of severe tissue
30 injury and lysis will not lead to a systemic and lethal pro-inflammatory cytokine cascade.

It is possible, therefore, that the α 2M receptor renders it possible for the APCs to sample (i) the extracellular milieu of the blood through α 2M and other plasma ligands and (ii) the intracellular milieu of the tissues through HSPs, particularly of the gp96 family. The former permits APCs to implement their primordial phagocytic function, while the latter
35 allows them to execute its innate and adaptive immunological functions. Viewed in another perspective, recognition of apoptotic cells by APCs through CD36 or phosphatidyl serine,

leads to anti-inflammatory signals, while interaction of the APC with necrotic cells through α 2M receptor leads to pro-inflammatory innate and adaptive immune responses (see Srivastava *et al.*, 1998, *Immunity* 8: 657-665).

5 The invention is not to be limited in scope by the specific embodiments described which are intended as single illustrations of individual aspects of the invention, and functionally equivalent methods and components are within the scope of the invention. Indeed various modifications of the invention, in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and 10 accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

 All references cited herein, including patent applications, patents, and other publications, are incorporated by reference herein in their entireties for all purposes.

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WHAT IS CLAIMED IS:

1. A method for identifying a compound that modulates an HSP- α 2M receptor-mediated process, comprising:
 - 5 (a) contacting a test compound with a heat shock protein and an alpha (2) macroglobulin receptor; and
 - (b) measuring the level of alpha (2) macroglobulin receptor activity or expression, such that if the level of activity or expression measured in (b) differs from the level of alpha (2) macroglobulin receptor activity in the absence of the test compound, then a compound
- 10 that modulates an HSP- α 2M receptor-mediated process is identified.
2. The method of Claim 1, in which the compound identified is an antagonist which interferes with the interaction of the heat shock protein with the alpha (2) macroglobulin receptor, further comprising the step of:
 - 15 (c) determining whether the level interferes with the interaction of the heat shock protein and the alpha (2) macroglobulin receptor.
3. The method of Claim 1, in which the test compound is an antibody specific for the alpha (2) macroglobulin receptor.
- 20 4. The method of Claim 1, in which the test compound is an antibody specific for alpha (2) macroglobulin.
5. The method of Claim 1, in which the test compound is an antibody specific for a heat shock protein.
- 25 6. The method of Claim 1, in which the test compound is a small molecule.
7. The method of Claim 1, in which the test compound is a peptide.
- 30 8. The method of Claim 7, in which the peptide comprises at least 5 consecutive amino acids of the alpha (2) macroglobulin receptor (SEQ ID NO.: 7).
9. The method of Claim 7, in which the peptide comprises at least 5 consecutive amino acids of alpha (2) macroglobulin (SEQ ID NO.: 4).

10. The method of Claim 7, in which the peptide comprises at least 5 consecutive amino acids of a heat shock protein sequence.

11. The method of Claim 1, in which the compound is an agonist which enhances 5 the interaction of the heat shock protein with the alpha (2) macroglobulin receptor.

12. The method of Claim 1 in which the HSP- α 2M receptor-mediated process affects an autoimmune disorder, a disease or disorder involving disruption of antigen presentation or endocytosis, a disease or disorder involving cytokine clearance or 10 inflammation, a proliferative disorder, a viral disorder or other infectious disease, hypercholesterolemia, Alzheimer's disease, diabetes, or osteoporosis.

13. A method for identifying a compound that modulates an HSP- α 2M receptor-mediated process, comprising:

15 (a) contacting a test compound with a heat shock protein and an alpha (2) macroglobulin receptor-expressing cell; and
(b) measuring the level of alpha (2) macroglobulin receptor activity or expression in the cell,

such that if the level of activity or expression measured in (b) differs from the level of alpha 20 (2) macroglobulin receptor activity in the absence of the test compound, then a compound that modulates an HSP- α 2M receptor-mediated process is identified.

14. The method of Claim 1 or 13 wherein the alpha (2) macroglobulin receptor activity measured is the ability to interact with a heat shock protein.

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15. The method of Claim 13 wherein the heat shock protein is non-covalently associated with an antigenic peptide and the alpha (2) macroglobulin receptor activity measured is the ability to re-present the antigenic peptide.

30 16. The method of Claim 13 wherein the heat shock protein is non-covalently associated with an antigenic peptide and the alpha (2) macroglobulin receptor activity measured is the ability to stimulate a cytotoxic T cell response against the antigenic peptide.

17. A method for identifying a compound that modulates the binding of a heat 35 shock protein to the α 2M receptor, comprising:

5 (a) contacting a heat shock protein with an alpha (2) macroglobulin receptor, or fragment, or analog, derivative or mimetic thereof, in the presence of a test compound; and

10 (b) measuring the amount of heat shock protein bound to the alpha (2)

15 macroglobulin receptor, or fragment, analog, derivative or mimetic thereof, such that if the amount of bound heat shock protein measured in (b) differs from the amount of bound heat shock protein measured in the absence of the test compound, then a compound that modulates the binding of an HSP to the α 2M receptor is identified.

20 18. The method of Claim 17 in which the alpha (2) macroglobulin receptor contacted in step (a) is on a cell surface.

25 19. The method of Claim 17 wherein the alpha (2) macroglobulin receptor is immobilized to a solid surface.

20 20. The method of Claim 19 wherein the solid surface is a microtiter dish.

25 21. The method of Claim 17 wherein the amount of bound heat shock protein is measured by contacting the cell with a heat shock protein-specific antibody.

20 22. The method of Claim 17 wherein the heat shock protein is labeled and the amount of bound heat shock protein is measured by detecting the label.

25 23. The method of Claim 22 wherein the heat shock protein is labeled with a fluorescent label.

20 24. A method for identifying a compound that modulates heat shock protein-mediated antigen presentation by alpha (2) macroglobulin receptor-expressing cells comprising:

30 (a) adding a test compound to a mixture of alpha (2) macroglobulin receptor-expressing cells and a complex consisting essentially of a heat shock protein noncovalently associated with an antigenic molecule, under conditions conducive to alpha (2) macroglobulin receptor-mediated endocytosis;

35 (b) measuring the level of stimulation of antigen-specific cytotoxic T cells by the alpha (2) macroglobulin receptor-expressing cells,

such that if the level measured in (b) differs from the level of said stimulation in the absence of the test compound, then a compound that modulates heat shock protein-mediated antigen presentation by alpha (2) macroglobulin receptor-expressing cells is identified.

5 25. The method of Claim 24, in which the measuring the level of the antigenic molecule presented on the cell surface of step (b) comprises:

- (i) adding the alpha (2) macroglobulin receptor-expressing cells formed in step (a) to T cells under conditions conducive to the activation of the T cells; and
- 10 (ii) comparing the level of activation of said cytotoxic T cells with the level of activation of T cells by an alpha (2) macroglobulin receptor-expressing cell formed in the absence of the test compound,
wherein an increase or decrease in level of T cell activation indicates that a compound that modulates heat shock protein-mediated antigen presentation by alpha (2) macroglobulin
15 receptor-expressing cells is identified.

26. The method of Claim 1, 18, or 24 in which the heat shock protein is gp96.

27. A method for detecting a heat shock protein-alpha (2) macroglobulin receptor-related disorder in a mammal comprising measuring the level of activity from an HSP-alpha (2) macroglobulin receptor-mediated process in a patient sample, such that if the measured level differs from the level found in clinically normal individuals, then a heat shock protein-alpha (2) macroglobulin receptor-related disorder is detected.

25 28. The method of Claim 27 comprising contacting a sample derived from a patient with an antibody specific for the alpha (2) macroglobulin receptor under conditions such that immunospecific binding by the antibody.

30 29. The method of Claim 27 comprising contacting a sample derived from a patient with an antibody specific for a heat shock protein under conditions such that immunospecific binding by the antibody.

35 30. The method of Claim 27 comprising contacting a sample derived from a patient with an antibody specific for an HSP- α 2M complex under conditions such that immunospecific binding by the antibody.

31. A method for modulating an immune response comprising administering to a mammal a purified compound that modulates the interaction of a heat shock protein with the alpha (2) macroglobulin receptor.

5 32. The method of Claim 31, in which the compound is an agonist which enhances the interaction of the heat shock protein and the alpha (2) macroglobulin receptor.

10 33. A method for treating an autoimmune disorder comprising administering to a mammal in need of such treatment a purified compound that interferes with the interaction of a heat shock protein with the alpha (2) macroglobulin receptor.

34. The method of Claim 31 or 33 in which the compound is an antagonist that interferes with the interaction between the heat shock protein and the $\alpha 2M$ receptor.

15 35. The method of Claim 34, in which the antagonist is an antibody specific for alpha (2) macroglobulin receptor.

36. The method of Claim 34, in which the antagonist is an antibody specific for a heat shock protein.

20 37. The method of Claim 34, in which the antagonist is a small molecule.

38. The method of Claim 34, in which the antagonist is a peptide.

25 39. The method of Claim 34, in which the peptide comprises at least 5 consecutive amino acids of alpha (2) macroglobulin receptor (SEQ ID NO.:1).

40. The method of Claim 34, in which the peptide comprises at least 5 consecutive amino acids of alpha (2) macroglobulin (SEQ ID NO.: 3).

30 41. The method of Claim 34, in which the peptide comprises at least 5 consecutive amino acids of a heat shock protein sequence.

42. A method for treating an autoimmune disorder comprising administering to a 35 mammal in need of such treatment a recombinant cell that expresses an alpha (2)

macroglobulin receptor which decreases the uptake of a heat shock protein by a functional alpha (2) macroglobulin receptor.

43. A method for increasing the immunopotency of a cancer cell or an infected
5 cell comprising transforming said cell with a nucleic acid comprising a nucleotide sequence
that (i) is operably linked to a promoter, and (ii) encodes an alpha (2) macroglobulin receptor
polypeptide.

44. A method for increasing the immunopotency of a cancer cell or an infected
10 cell comprising:

- (a) transforming said cell with a nucleic acid comprising a nucleotide sequence
that (i) is operably linked to a promoter, and (ii) encodes an alpha (2)
macroglobulin receptor polypeptide, and
- (b) administering said cell to an individual in need of treatment,
15 so as to obtain an elevated immune response.

45. A recombinant cancer cell transformed with a nucleic acid comprising a
nucleotide sequence that (i) is operably linked to a promoter, and (ii) encodes an alpha (2)
macroglobulin receptor polypeptide.

20 46. A recombinant infected cell transformed with a nucleic acid comprising a
nucleotide sequence that (i) is operably linked to a promoter, and (ii) encodes an alpha (2)
macroglobulin receptor polypeptide.

25 47. The recombinant cell of Claim 45 or 46 which is a human cell.

48. A kit, comprising in one or more containers: (a) an anti- α 2M receptor
antibody or a nucleic acid probe capable of hybridizing to an α 2M receptor nucleic acid, (b) a
purified heat shock protein, nucleic acid encoding a heat shock protein, or cell expressing a
30 heat shock protein; and (c) instructions for use in detecting a heat shock protein-alpha (2)
macroglobulin receptor-related disorder.

49. The kit of Claim 48 wherein the antibody or nucleic acid probe is labeled with
a detectable marker.

50. The kit of Claim 48 further comprising a labeled macroglobulin receptor polypeptide.

51. A kit, in one or more containers, comprising: (a) a purified heat shock protein, nucleic acid encoding a heat shock protein, or cell expressing a heat shock protein; and (b) an alpha (2) macroglobulin receptor polypeptide, nucleic acid encoding an alpha (2) macroglobulin receptor polypeptide, or cell expressing an alpha (2) macroglobulin receptor polypeptide.

10 52. The kit of Claim 51 in which the alpha (2) macroglobulin receptor polypeptide, nucleic acid encoding an alpha (2) macroglobulin receptor polypeptide, or cell expressing an alpha (2) macroglobulin receptor polypeptide is purified.

15 53. The kit of Claim 51 further comprising instructions for use in treating an autoimmune disorder, an infectious disease, or a proliferative disorder.

54. A method for identifying an α 2M receptor fragment capable of binding a heat shock protein, said method comprising:

20 (a) contacting a heat shock protein, or peptide-binding fragment thereof, with one or more alpha (2) macroglobulin receptor fragments; and
(b) identifying an α 2M receptor fragment which specifically binds to the heat shock protein, or peptide-binding fragment thereof.

25 55. A method for identifying an α 2M receptor fragment capable of inducing an HSP- α 2M receptor-mediated process, said method comprising:

(a) contacting a heat shock protein with a cell expressing α 2M receptor fragment; and
(b) measuring the level of alpha (2) macroglobulin receptor activity in the cell, such that if the level of the HSP- α 2M receptor-mediated process or activity measured in (b) 30 is greater than the level of alpha (2) macroglobulin receptor activity in the absence of the α 2M receptor fragment, then an α 2M receptor fragment capable of inducing an HSP- α 2M receptor-mediated process is identified.

35 56. The method of Claim 55 wherein the alpha (2) macroglobulin receptor activity measured is the ability to interact with the heat shock protein.

57. The method of Claim 55 wherein the heat shock protein is non-covalently associated with an antigenic peptide and the alpha (2) macroglobulin receptor activity measured is the ability to re-present the antigenic peptide.

5 58. The method of Claim 55 wherein the heat shock protein is non-covalently associated with an antigenic peptide and the alpha (2) macroglobulin receptor activity measured is the ability to stimulate a cytotoxic T cell response against the antigenic peptide.

10 59. A method for identifying a heat shock protein fragment capable of binding an α 2M receptor, said method comprising:

- (a) contacting an α 2M receptor with one or more heat shock protein fragments; and
- (b) identifying a heat shock protein fragment which specifically binds to the α 2M receptor.

15 60. A method for identifying a heat shock protein fragment capable of inducing an HSP- α 2M receptor-mediated process, said method comprising:

- (a) contacting an α 2M receptor fragment with a cell expressing a heat shock protein; and
- (b) measuring the level of alpha (2) macroglobulin receptor activity in the cell, such that if the level of the HSP- α 2M receptor-mediated process or activity measured in (b) is greater than the level of alpha (2) macroglobulin receptor activity in the absence of said heat shock protein fragment, then a heat shock protein fragment capable of inducing an HSP- α 2M receptor-mediated process is identified.

25 61. The method of Claim 60 wherein the alpha (2) macroglobulin receptor activity measured is the ability to interact with the heat shock protein fragment.

30 62. The method of Claim 60 wherein the heat shock protein fragment is non-covalently associated with an antigenic peptide and the alpha (2) macroglobulin receptor activity measured is the ability to re-present the antigenic peptide.

35 63. The method of Claim 60 wherein the heat shock protein fragment is non-covalently associated with an antigenic peptide and the alpha (2) macroglobulin receptor activity measured is the ability to stimulate a cytotoxic T cell response against the antigenic peptide.

ABSTRACT

The present invention relates to the use of alpha (2) macroglobulin ("α2M") receptor
5 as a heat shock protein receptor, cells that express the α2M receptor bound to an HSP, and
antibodies and other molecules that bind the α2M receptor-HSP complex. The invention also
relates to screening assays to identify compounds that modulate the interaction of an HSP
with the α2M receptor, and methods for using compositions comprising α2M-receptor
sequences for the diagnosis and treatment of immune disorders, proliferative disorders, and
10 infectious diseases.

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(SHEET / OF 81)

FITC-SA

FITC-SP96

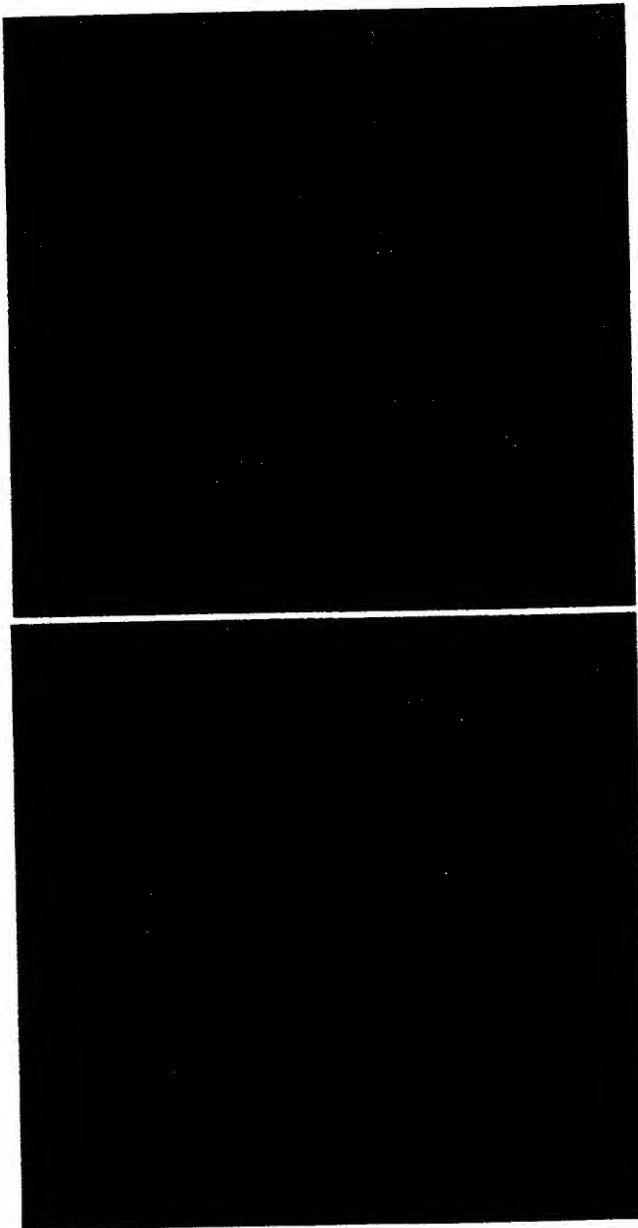


FIG. 1a

Membranes from RAW264.7 P815Affinity column gp96 SA gp96

212 ■

116 ■

83 ■

51 ■

35 ■

28 ■

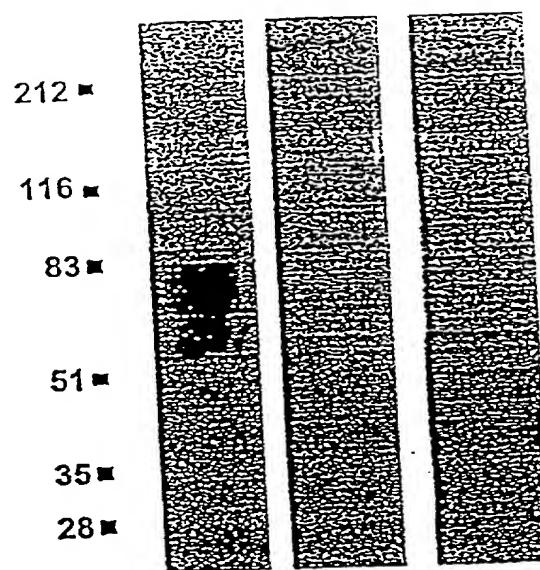


FIG. 1b

	Cells	MO	MO	MO	P815
125I-SASD-gp96	+	+	+	+	+
UV	+	-	+	+	
2-ME	+	+	-	+	

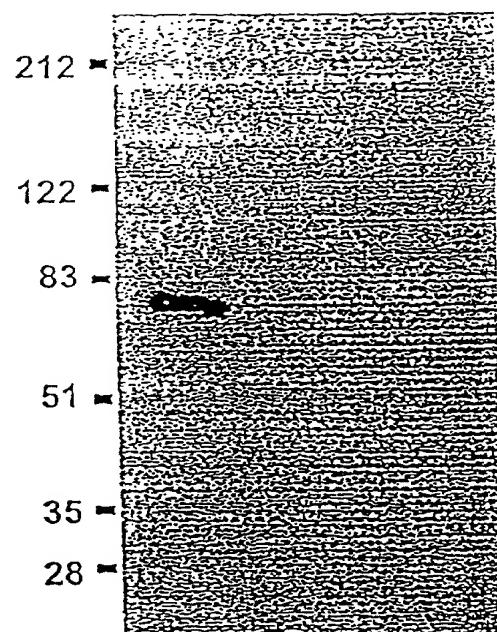


FIG. 1c

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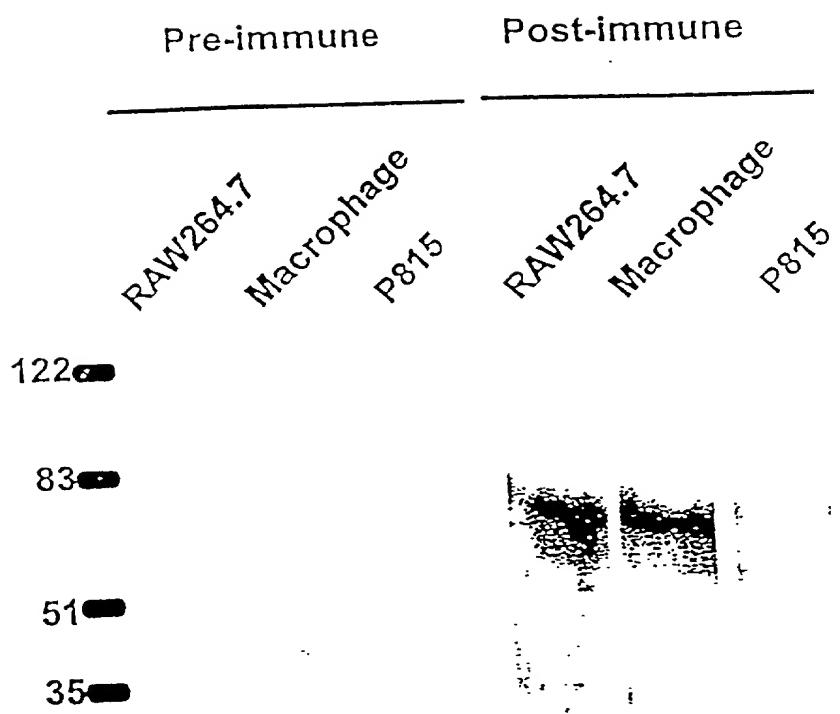


FIG. 2a

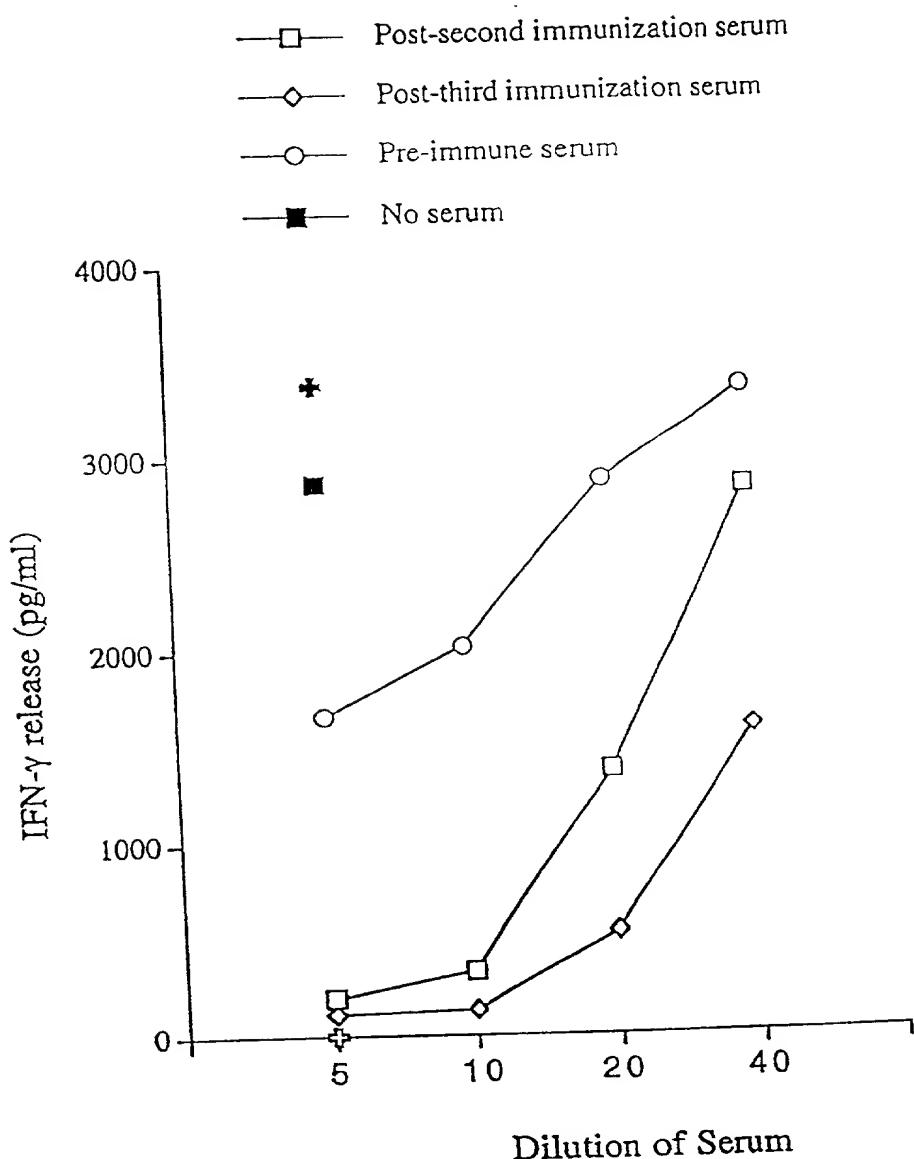


FIG. 2b

Seq #	b	y	+1
G 1	58.1	-	--
G 2	115.1	1095.2	10
A 3	186.2	1038.2	9
L 4	299.3	967.1	8
H 5	436.5	853.9	7
I 6	549.6	716.8	6
Y 7	712.8	603.6	5
H 8	850.0	440.5	4
Q 9	978.1	303.3	3
R 10	-	175.2	2
			1

FIG. 3a

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B

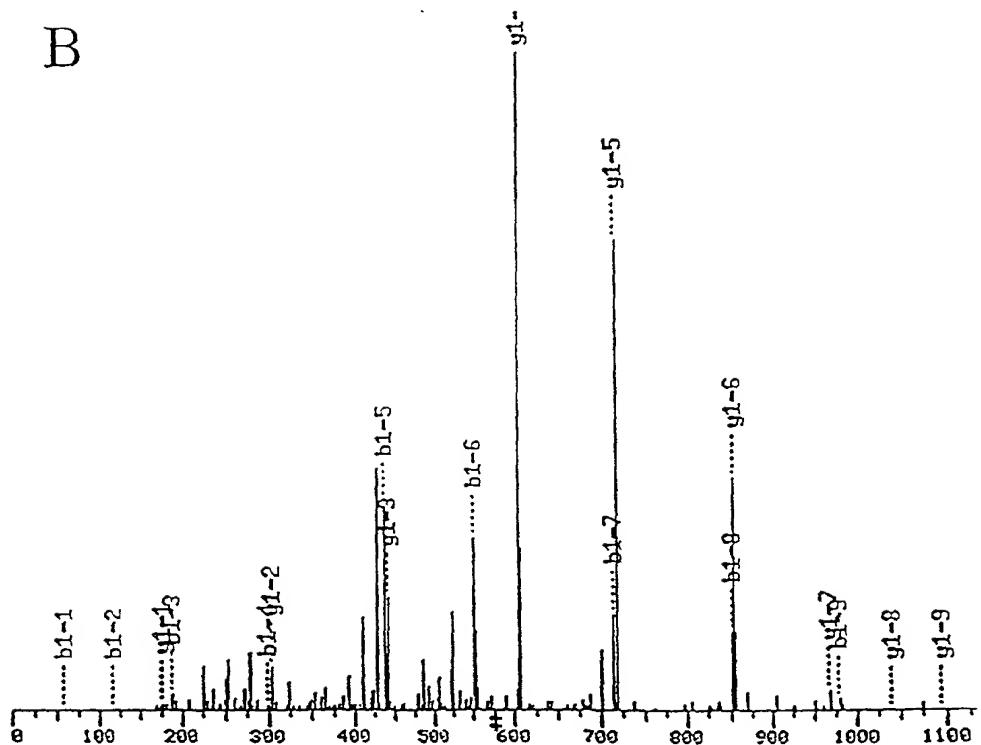
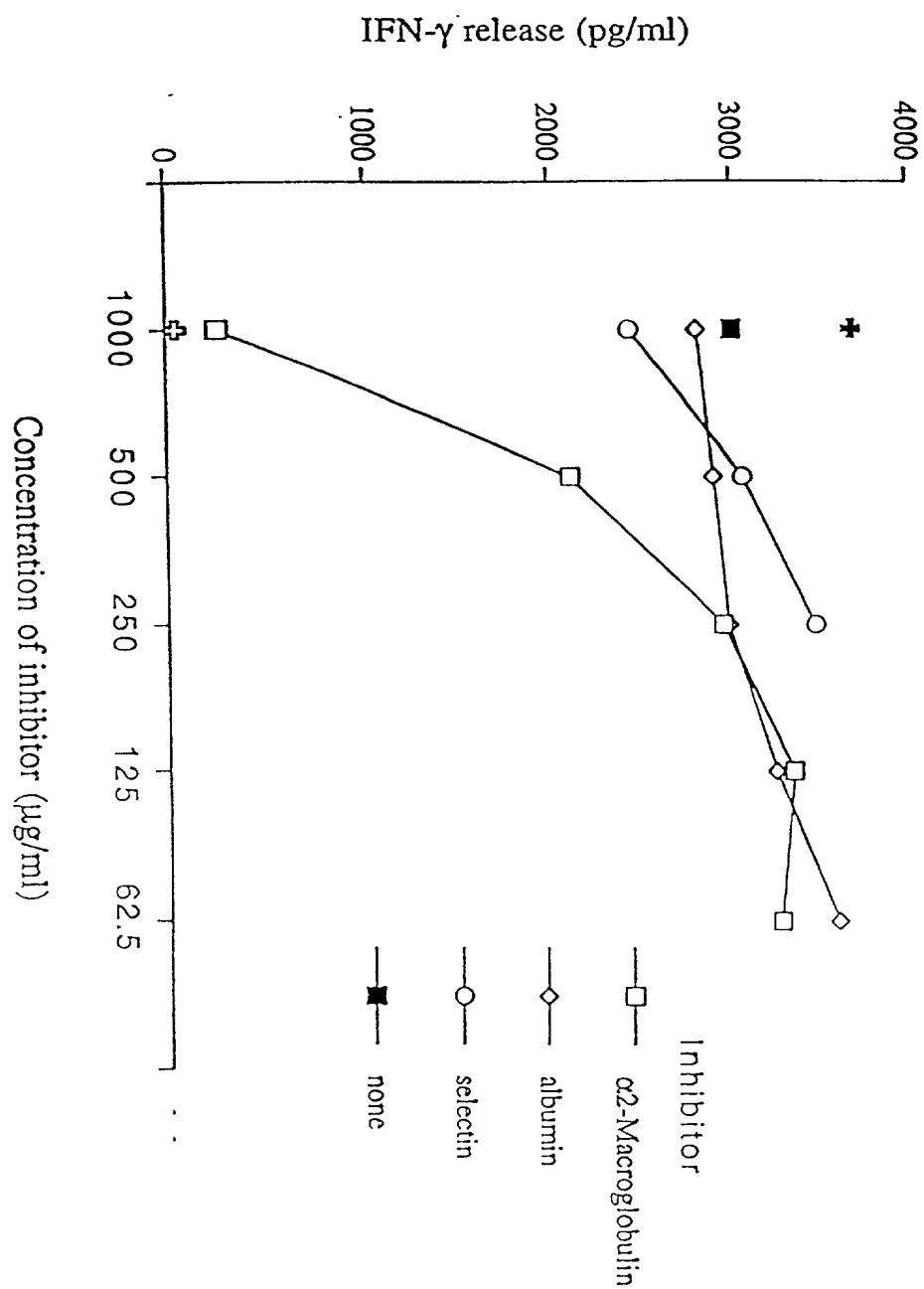


FIG. 3b

Position	MH+	Sequence
509-518	955.0122	SGFSLGSDGK (Seq 10 No: 54)
328-337	973.1753	GIALDPAMGK (Seq 10 No: 55)
460-469	1152.3010	GGALHIYHQR (Seq 10 No: 56)
338-348	1315.5116	VFFTDYQIIPK (Seq 10 No: 57)

FIG. 3c



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FIG. 4

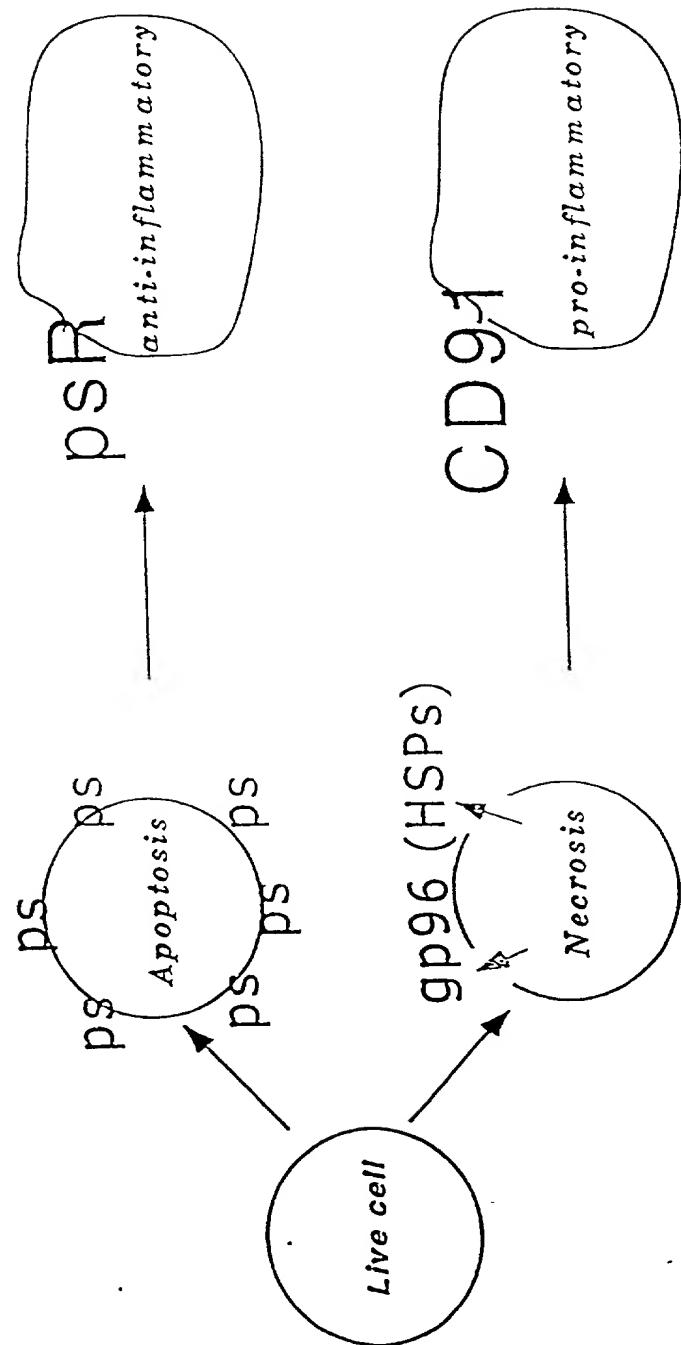


FIG. 5

CGCTGCTCCC CGCCAGTGCA	CTGAGGGAGGC	GGAAACGGGG	GAGCCCTAG	TGCTCCATCA	60
GGCCCCCTACC AAGGCACCCC	CATCGGGTCC	ACGCCCCCCCA	CCCCCCACCC	CGCCTCCTCC	120
CAATTGTGCA TTTTGTCAGC	CGGAGTCGGC	TCCGAGATGG	GGCTGTGAGC	TTCGCCCTGG	180
GAGGGGGAGA GGAGCGAGGA	GTAAAGCAGG	GGTGAAGGGT	TCGAATTG	GGGCAGGGGG	240
CGCACCCGCG TCAGCAGGCC	CTTCCCAGGG	GGCTCGGAAC	TGTACCATTT	CACCTATGCC	300
CCTGGTTCGC TTTGCTTAAG	GAAGGATAAG	ATAGAAGAGT	CGGGGAGAGG	AAGATAAAAGG	360
GGGACCCCCC AATTGGGGGG	GGCGAGGACA	AGAAGTAACA	GGACCAGAGG	GTGGGGGCTG	420
CTGTTGCAT CGGCCACAC	C ATG CTG ACC CCG	TTG CTG CTG CTC GTG			471
	Met Leu Thr Pro Pro	Leu Leu Leu Leu Val			
	1	5	10		
CCG CTG CTT TCA GCT CTG GTC TCC GGG GCC ACT ATG GAT GCC CCT AAA				519	
Pro Leu Leu Ser Ala Leu Val Ser Gly Ala Thr Met Asp Ala Pro Lys					
15	20	25			
ACT TGC AGC CCT AAG CAG TTT GCC TGC AGA GAC CAA ATC ACC TGT ATC				567	
Thr Cys Ser Pro Lys Gln Phe Ala Cys Arg Asp Gln Ile Thr Cys Ile					
30	35	40			
TCA AAG GGC TGG CGG TGT GAC GGT GAA AGA GAT TGC CCC GAC GGC TCT				615	
Ser Lys Gly Trp Arg Cys Asp Gly Glu Arg Asp Cys Pro Asp Gly Ser					
45	50	55			
GAT GAA GCC CCT GAG ATC TGT CCA CAG AGT AAA GCC CAG AGA TGC CCG				663	
Asp Glu Ala Pro Glu Ile Cys Pro Gln Ser Lys Ala Gln Arg Cys Pro					
60	65	70			
CCA AAT GAG CAC AGT TGT CTG GGG ACT GAG CTA TGT GTC CCC ATG TCT				711	
Pro Asn Glu His Ser Cys Leu Gly Thr Glu Leu Cys Val Pro Met Ser					
75	80	85	90		
CGT CTC TGC AAC GGG ATC CAG GAC TGC ATG GAT GGC TCA GAC GAG GGT				759	
Arg Leu Cys Asn Gly Ile Gln Asp Cys Met Asp Gly Ser Asp Glu Gly					
95	100	105			
GCT CAC TGC CGA GAG CTC CGA GCC AAC TGT TCT CGA ATG GGT TGT CAA				807	
Ala His Cys Arg Glu Leu Arg Ala Asn Cys Ser Arg Met Gly Cys Gln					
110	115	120			
CAC CAT TGT GTA CCT ACA CCC AGT GGG CCC ACG TGC TAC TGT AAC AGC				855	
His His Cys Val Pro Thr Pro Ser Gly Pro Thr Cys Tyr Cys Asn Ser					
125	130	135			
AGC TTC CAG CTC GAG GCA GAT GGC AAG ACG TGC AAA GAT TTT GAC GAG				903	
Ser Phe Gln Leu Glu Ala Asp Gly Lys Thr Cys Lys Asp Phe Asp Glu					
140	145	150			
TGT TCC GTG TAT GGC ACC TGC AGC CAG CTT TGC ACC AAC ACA GAT GGC				951	
Cys Ser Val Tyr Gly Thr Cys Ser Gln Leu Cys Thr Asn Thr Asp Gly					
155	160	165	170		
TCC TTC ACA TGT GGC TGT GTT GAA GGC TAC CTG CTG CAA CCG GAC AAC				999	
Ser Phe Thr Cys Gly Cys Val Glu Gly Tyr Leu Leu Gln Pro Asp Asn					
175	180	185			
CGC TCC TGC AAG GCC AAG AAT GAG CCA GTA GAT CGG CCG CCA GTG CTA				1047	
Arg Ser Cys Lys Ala Lys Asn Glu Pro Val Asp Arg Pro Pro Val Leu					
190	195	200			

FIG. 6a

CTG ATT GCC AAC TCT CAG AAC ATC CTA GCT ACG TAC CTG AGT GGG GCC Leu Ile Ala Asn Ser Gln Asn Ile Leu Ala Thr Tyr Leu Ser Gly Ala 205 210 215	1095
CAA GTG TCT ACC ATC ACA CCC ACC AGC ACC CGA CAA ACC ACG GCC ATG Gln Val Ser Thr Ile Thr Pro Thr Ser Thr Arg Gln Thr Thr Ala Met 220 225 230	1143
GAC TTC AGT TAT GCC AAT GAG ACC GTA TGC TGG GTG CAC GTT GGG GAC Asp Phe Ser Tyr Ala Asn Glu Thr Val Cys Trp Val His Val Gly Asp 235 240 245 250	1191
AGT GCT GCC CAG ACA CAG CTC AAG TGT GCC CGG ATG CCT GGC CTG AAG Ser Ala Ala Gln Thr Gln Leu Lys Cys Ala Arg Met Pro Gly Leu Lys 255 260 265	1239
GGC TTT GTG GAT GAG CAT ACC ATC AAC ATC TCC CTC AGC CTG CAC CAC Gly Phe Val Asp Glu His Thr Ile Asn Ile Ser Leu Ser Leu His His 270 275 280	1287
GTG GAG CAG ATG GCA ATC GAC TGG CTG ACG GGA AAC TTC TAC TTT GTC Val Glu Gln Met Ala Ile Asp Trp Leu Thr Gly Asn Phe Tyr Phe Val 285 290 295	1335
GAC GAC ATT GAC GAC AGG ATC TTT GTC TGT AAC CGA AAC GGG GAC ACC Asp Asp Ile Asp Asp Arg Ile Phe Val Cys Asn Arg Asn Gly Asp Thr 300 305 310	1383
TGT GTC ACT CTG CTG GAC CTG GAA CTC TAC AAC CCC AAA GGC ATC GCC Cys Val Thr Leu Leu Asp Leu Glu Leu Tyr Asn Pro Lys Gly Ile Ala 315 320 325 330	1431
TTG GAC CCC GCC ATG GGG AAG GTG TTC TTC ACT GAC TAC GGG CAG ATC Leu Asp Pro Ala Met Gly Lys Val Phe Phe Thr Asp Tyr Gly Gln Ile 335 340 345	1479
CCA AAG GTG GAG CGC TGT GAC ATG GAT GGA CAG AAC CGC ACC AAG CTG Pro Lys Val Glu Arg Cys Asp Met Asp Gly Gln Asn Arg Thr Lys Leu 350 355 360	1527
GTG GAT AGC AAG ATC GTG TTT CCA CAC GGC ATC ACC CTG GAC CTG GTC Val Asp Ser Lys Ile Val Phe Pro His Gly Ile Thr Leu Asp Leu Val 365 370 375	1575
AGC CGC CTC GTC TAC TGG GCG GAC GCC TAC CTA GAC TAC ATC GAG GTG Ser Arg Leu Val Tyr Trp Ala Asp Ala Tyr Leu Asp Tyr Ile Glu Val 380 385 390	1623
GTA GAC TAC GAA GGG AAG GGT CGG CAG ACC ATC ATC CAA GGC ATC CTG Val Asp Tyr Glu Gly Lys Gly Arg Gln Thr Ile Ile Gln Gly Ile Leu 395 400 405 410	1671
ATC GAG CAC CTG TAC GGC CTG ACC GTG TTT GAG AAC TAT CTC TAC GCC Ile Glu His Leu Tyr Gly Leu Thr Val Phe Glu Asn Tyr Leu Tyr Ala 415 420 425	1719
ACC AAC TCG GAC AAT GCC AAC ACG CAG CAG AAG ACG AGC GTG ATC CGA Thr Asn Ser Asp Asn Ala Asn Thr Gln Gln Lys Thr Ser Val Ile Arg 430 435 440	1767

FIG. 6a

GTG AAC CGG TTC AAC AGT ACT GAG TAC CAG GTC GTC ACC CGT GTG GAC Val Asn Arg Phe Asn Ser Thr Glu Tyr Gln Val Val Thr Arg Val Asp 445 450 455	1815
AAG GGT GGT GCC CTG CAT ATC TAC CAC CAG CGA CGC CAG CCC CGA GTG Lys Gly Gly Ala Leu His Ile Tyr His Gln Arg Arg Gln Pro Arg Val 460 465 470	1863
CGG AGT CAC GCC TGT GAG AAT GAC CAG TAC GGG AAG CCA GGT GGC TGC Arg Ser His Ala Cys Glu Asn Asp Gln Tyr Gly Lys Pro Gly Gly Cys 475 480 485 490	1911
TCC GAC ATC TGC CTC CTG GCC AAC AGT CAC AAG GCA AGG ACC TGC AGG Ser Asp Ile Cys Leu Leu Ala Asn Ser His Lys Ala Arg Thr Cys Arg 495 500 505	1959
TGC AGG TCT GGC TTC AGC CTG GGA AGT GAT GGG AAG TCT TGT AAG AAA Cys Arg Ser Gly Phe Ser Leu Gly Ser Asp Gly Lys Ser Cys Lys Lys 510 515 520	2007
CCT GAA CAT GAG CTG TTC CTC GTG TAT GGC AAG GGC CGA CCA GGC ATC Pro Glu His Glu Leu Phe Leu Val Tyr Gly Lys Gly Arg Pro Gly Ile 525 530 535	2055
ATT AGA GGC ATG GAC ATG GGG GCC AAG GTC CCA GAT GAG CAC ATG ATC Ile Arg Gly Met Asp Met Gly Ala Lys Val Pro Asp Glu His Met Ile 540 545 550	2103
CCC ATC GAG AAC CTT ATG AAT CCA CGC GCT CTG GAC TTC CAC GCC GAG Pro Ile Glu Asn Leu Met Asn Pro Arg Ala Leu Asp Phe His Ala Glu 555 560 565 570	2151
ACC GGC TTC ATC TAC TTT GCT GAC ACC ACC AGC TAC CTC ATT GGC CGC Thr Gly Phe Ile Tyr Phe Ala Asp Thr Thr Ser Tyr Leu Ile Gly Arg 575 580 585	2199
CAG AAA ATT GAT GGC ACG GAG AGA GAG ACT ATC CTG AAG GAT GGC ATC Gln Lys Ile Asp Gly Thr Glu Arg Glu Thr Ile Leu Lys Asp Gly Ile 590 595 600	2247
CAC AAT GTG GAG GGC GTA GCC GTG GAC TGG ATG GGA GAC AAT CTT TAC His Asn Val Glu Gly Val Ala Val Asp Trp Met Gly Asp Asn Leu Tyr 605 610 615	2295
TGG ACT GAT GAT GGC CCC AAG AAG ACC ATT AGT GTG GCC AGG CTG GAG Trp Thr Asp Asp Gly Pro Lys Lys Thr Ile Ser Val Ala Arg Leu Glu 620 625 630	2343
AAA GCC GCT CAG ACC CGG AAG ACT CTA ATT GAG GGC AAG ATG ACA CAC Lys Ala Ala Gln Thr Arg Lys Thr Leu Ile Glu Gly Lys Met Thr His 635 640 645 650	2391
CCC AGG GCC ATT GTA GTG GAT CCA CTC AAT GGG TGG ATG TAC TGG ACA Pro Arg Ala Ile Val Val Asp Pro Leu Asn Gly Trp Met Tyr Trp Thr 655 660 665	2439
GAC TGG GAG GAG GAC CCC AAG GAC AGT CGG CGA GGG CGG CTC GAG AGG Asp Trp Glu Glu Asp Pro Lys Asp Ser Arg Arg Gly Arg Leu Glu Arg 670 675 680	2487

FIG. 6a

GCT TGG ATG GAC GGC TCA CAC CGA GAT ATC TTT GTC ACC TCC AAG ACA Ala Trp Met Asp Gly Ser His Arg Asp Ile Phe Val Thr Ser Lys Thr 685 690 695	2535
GTG CTT TGG CCC AAT GGG CTA AGC CTG GAT ATC CCA GCC GGA CGC CTC Val Leu Trp Pro Asn Gly Leu Ser Leu Asp Ile Pro Ala Gly Arg Leu 700 705 710	2583
TAC TGG GTG GAT GCC TTC TAT GAC CGA ATT GAG ACC ATA CTG CTC AAT Tyr Trp Val Asp Ala Phe Tyr Asp Arg Ile Glu Thr Ile Leu Leu Asn 715 720 725 730	2631
GCC ACA GAC CGG AAG ATT GTA TAT GAG GGT CCT GAA CTG AAT CAT GCC Gly Thr Asp Arg Lys Ile Val Tyr Glu Gly Pro Glu Leu Asn His Ala 735 740 745	2679
TTC GGC CTG TGT CAC CAT GGC AAC TAC CTC TTT TGG ACC GAG TAC CGG Phe Gly Leu Cys His His Gly Asn Tyr Leu Phe Trp Thr Glu Tyr Arg 750 755 760	2727
AGC GGC AGC GTC TAC CGC TTG GAA CGG GGC GTG GCA GGC GCA CCG CCC Ser Gly Ser Val Tyr Arg Leu Glu Arg Gly Val Ala Gly Ala Pro Pro 765 770 775	2775
ACT GTG ACC CTT CTG CGC AGC GAG AGA CCG CCT ATC TTT GAG ATC CGA Thr Val Thr Leu Leu Arg Ser Glu Arg Pro Pro Ile Phe Glu Ile Arg 780 785 790	2823
ATG TAC GAC GCG CAC GAG CAG CAA GTG GGT ACC AAC AAA TGC CGG GTA Met Tyr Asp Ala His Glu Gln Gln Val Gly Thr Asn Lys Cys Arg Val 795 800 805 810	2871
AAT AAC GGA GGC TGC AGC AGC CTG TGC CTC GCC ACC CCC GGG AGC CGC Asn Asn Gly Gly Cys Ser Ser Leu Cys Leu Ala Thr Pro Gly Ser Arg 815 820 825	2919
CAG TGT GCC TGT GCC GAG GAC CAG GTG TTG GAC ACA GAT GGT GTC ACC Gln Cys Ala Cys Ala Glu Asp Gln Val Leu Asp Thr Asp Gly Val Thr 830 835 840	2967
TGC TTG GCG AAC CCA TCC TAC GTG CCC CCA CCC CAG TGC CAG CCG GGC Cys Leu Ala Asn Pro Ser Tyr Val Pro Pro Pro Gln Cys Gln Pro Gly 845 850 855	3015
CAG TTT GCC TGT GCC AAC AAC CGC TGC ATC CAG GAG CGC TGG AAG TGT Gln Phe Ala Cys Ala Asn Asn Arg Cys Ile Gln Glu Arg Trp Lys Cys 860 865 870	3063
GAC GGA GAC AAC GAC TGT CTG GAC AAC AGC GAT GAG GCC CCA GCA CTG Asp Gly Asp Asn Asp Cys Leu Asp Asn Ser Asp Glu Ala Pro Ala Leu 875 880 885 890	3111
TGC CAT CAA CAC ACC TGT CCC TCG GAC CGA TTC AAG TGT GAG AAC AAC Cys His Gln His Thr Cys Pro Ser Asp Arg Phe Lys Cys Glu Asn Asn 895 900 905	3159
CGG TGT ATC CCC AAC CGC TGG CTC TGT GAT GGG GAT AAT GAT TGT GGC Arg Cys Ile Pro Asn Arg Trp Leu Cys Asp Gly Asp Asn Asp Cys Gly 910 915 920	3207

FIG. 6a

AAC AGC GAG GAC GAA TCC AAT GCC ACG TGC TCA GCC CGC ACC TGT CCA	3255
Asn Ser Glu Asp Glu Ser Asn Ala Thr Cys Ser Ala Arg Thr Cys Pro	
925 930 935	
CCC AAC CAG TTC TCC TGT GCC AGT GGC CGA TGC ATT CCT ATC TCA TGG	3303
Pro Asn Gln Phe Ser Cys Ala Ser Gly Arg Cys Ile Pro Ile Ser Trp	
940 945 950	
ACC TGT GAT CTG GAT GAC TGT GGG GAC CGG TCC GAT GAG TCA GCC	3351
Thr Cys Asp Leu Asp Asp Cys Gly Asp Arg Ser Asp Glu Ser Ala	
955 960 965 970	
TCA TGC GCC TAC CCC ACC TGC TTC CCC CTG ACT CAA TTT ACC TGC AAC	3399
Ser Cys Ala Tyr Pro Thr Cys Phe Pro Leu Thr Gln Phe Thr Cys Asn	
975 980 985	
AAT GGC AGA TGT ATT AAC ATC AAC TGG CGG TGT GAC AAC GAC AAT GAC	3447
Asn Gly Arg Cys Ile Asn Ile Asn Trp Arg Cys Asp Asn Asp Asn Asp	
990 995 1000	
TGT GGG GAC AAC AGC GAC GAA GCC GGC TGC AGT CAC TCC TGC TCC AGT	3495
Cys Gly Asp Asn Ser Asp Glu Ala Gly Cys Ser His Ser Cys Ser Ser	
1005 1010 1015	
ACC CAG TTC AAG TGC AAC AGT GGC AGA TGC ATC CCC GAG CAC TGG ACG	3543
Thr Gln Phe Lys Cys Asn Ser Gly Arg Cys Ile Pro Glu His Trp Thr	
1020 1025 1030	
TGT GAT GGG GAC AAT GAT TGT GGG GAC TAC AGC GAC GAG ACA CAC GCC	3591
Cys Asp Gly Asp Asn Asp Cys Gly Asp Tyr Ser Asp Glu Thr His Ala	
1035 1040 1045 1050	
AAC TGT ACC AAC CAG GCT ACA AGA CCT CCT GGT GGC TGC CAC TCG GAT	3639
Asn Cys Thr Asn Gln Ala Thr Arg Pro Pro Gly Gly Cys His Ser Asp	
1055 1060 1065	
GAG TTC CAG TGC CCG CTA GAT GGC CTG TGC ATC CCC CTG AGG TGG CGC	3687
Glu Phe Gln Cys Pro Leu Asp Gly Leu Cys Ile Pro Leu Arg Trp Arg	
1070 1075 1080	
TGC GAC GGG GAC ACC GAC TGC ATG GAT TCC AGC GAT GAG AAG AGC TGT	3735
Cys Asp Gly Asp Thr Asp Cys Met Asp Ser Ser Asp Glu Lys Ser Cys	
1085 1090 1095	
GAG GGC GTG ACC CAT GTT TGT GAC CCG AAT GTC AAG TTT GGC TGC AAG	3783
Glu Gly Val Thr His Val Cys Asp Pro Asn Val Lys Phe Gly Cys Lys	
1100 1105 1110	
GAC TCC GCC CGG TGC ATC AGC AAG GCG TGG GTG TGT GAT GGC GAC AGC	3831
Asp Ser Ala Arg Cys Ile Ser Lys Ala Trp Val Cys Asp Gly Asp Ser	
1115 1120 1125 1130	
GAC TGT GAA GAT AAC TCC GAC GAG GAG AAC TGT GAG GGC CTG GCC TGC	3879
Asp Cys Glu Asp Asn Ser Asp Glu Glu Asn Cys Glu Ala Leu Ala Cys	
1135 1140 1145	
AGG CCA CCC TCC CAT CCC TGC GCC AAC AAC ACC TCT GTC TGC CTG CCT	3927
Arg Pro Pro Ser His Pro Cys Ala Asn Asn Thr Ser Val Cys Leu Pro	
1150 1155 1160	

CCT GAC AAG CTG TGC GAC GGC AAG GAT GAC TGT GGA GAC GGC TCG GAT Pro Asp Lys Leu Cys Asp Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp 1165 1170 1175	3975
GAG GGC GAG CTC TGT GAC CAG TGT TCT CTG AAT AAT GGT GGC TGT AGT Glu Gly Glu Leu Cys Asp Gln Cys Ser Leu Asn Asn Gly Gly Cys Ser 1180 1185 1190	4023
CAC AAC TGC TCA GTG GCC CCT GGT GAA GGC ATC GTG TGC TCT TGC CCT His Asn Cys Ser Val Ala Pro Gly Glu Gly Ile Val Cys Ser Cys Pro 1195 1200 1205 1210	4071
CTG GGC ATG GAG CTG GGC TCT GAC AAC CAC ACC TGC CAG ATC CAG AGC Leu Gly Met Glu Leu Gly Ser Asp Asn His Thr Cys Gln Ile Gln Ser 1215 1220 1225	4119
TAC TGT GCC AAG CAC CTC AAA TGC AGC CAG AAG TGT GAC CAG AAC AAG Tyr Cys Ala Lys His Leu Lys Cys Ser Gln Lys Cys Asp Gln Asn Lys 1230 1235 1240	4167
TTC AGT GTG AAG TGC TCC TGC TAC GAG GGC TGG GTC TTG GAG CCT GAC Phe Ser Val Lys Cys Ser Cys Tyr Glu Gly Trp Val Leu Glu Pro Asp 1245 1250 1255	4215
GGG GAA ACG TGC CGC AGT CTG GAT CCC TTC AAA CTG TTC ATC ATC TTC Gly Glu Thr Cys Arg Ser Leu Asp Pro Phe Lys Leu Phe Ile Ile Phe 1260 1265 1270	4263
TCC AAC CGC CAC GAG ATC AGG CGC ATT GAC CTT CAC AAG GGG GAC TAC Ser Asn Arg His Glu Ile Arg Arg Ile Asp Leu His Lys Gly Asp Tyr 1275 1280 1285 1290	4311
AGC GTC CTA GTG CCT GGC CTG CGC AAC ACT ATT GCC CTG GAC TTC CAC Ser Val Leu Val Pro Gly Leu Arg Asn Thr Ile Ala Leu Asp Phe His 1295 1300 1305	4359
CTC AGC CAG AGT GCC CTC TAC TGG ACC GAC GCG GTA GAG GAC AAG ATC Leu Ser Gln Ser Ala Leu Tyr Trp Thr Asp Ala Val Glu Asp Lys Ile 1310 1315 1320	4407
TAC CGT GGG AAA CTC CTG GAC AAC GGA GCC CTG ACC AGC TTT GAG GTG Tyr Arg Gly Lys Leu Leu Asp Asn Gly Ala Leu Thr Ser Phe Glu Val 1325 1330 1335	4455
GTG ATT CAG TAT GGC TTG GCC ACA CCA GAG GGC CTG GCT GTA GAT TGG Val Ile Gln Tyr Gly Leu Ala Thr Pro Glu Gly Leu Ala Val Asp Trp 1340 1345 1350	4503
ATT GCA GGC AAC ATC TAC TGG GTG GAG AGC AAC CTG GAC CAG ATC GAA Ile Ala Gly Asn Ile Tyr Trp Val Glu Ser Asn Leu Asp Gln Ile Glu 1355 1360 1365 1370	4551
GTG GCC AAG CTG GAC GGA ACC CTC CGA ACC ACT CTG CTG GCG GGT GAC Val Ala Lys Leu Asp Gly Thr Leu Arg Thr Thr Leu Leu Ala Gly Asp 1375 1380 1385	4599
ATT GAG CAC CCG AGG GCC ATC GCT CTG GAC CCT CGG GAT GGG ATT CTG Ile Glu His Pro Arg Ala Ile Ala Leu Asp Pro Arg Asp Gly Ile Leu 1390 1395 1400	4647

FIG. 6a

TTT TGG ACA GAC TGG GAT GCC AGC CTG CCA CGA ATC GAG GCT GCA TCC Phe Trp Thr Asp Trp Asp Ala Ser Leu Pro Arg Ile Glu Ala Ala Ser 1405 1410 1415	4695
ATG AGT GGA GCT GGC CGC CGA ACC ATC CAC CGG GAG ACA GGC TCT GGG Met Ser Gly Ala Gly Arg Arg Thr Ile His Arg Glu Thr Gly Ser Gly 1420 1425 1430	4743
GGC TGC GCC AAT GGG CTC ACC GTG GAT TAC CTG GAG AAG CGC ATC CTC Gly Cys Ala Asn Gly Leu Thr Val Asp Tyr Leu Glu Lys Arg Ile Leu 1435 1440 1445 1450	4791
TGG ATT GAT GCT AGG TCA GAT GCC ATC TAT TCA GCC CGG TAT GAC GGC Trp Ile Asp Ala Arg Ser Asp Ala Ile Tyr Ser Ala Arg Tyr Asp Gly 1455 1460 1465	4839
TCC GGC CAC ATG GAG GTG CTT CGG GGA CAC GAG TTC CTG TCA CAC CCA Ser Gly His Met Glu Val Leu Arg Gly His Glu Phe Leu Ser His Pro 1470 1475 1480	4887
TTT GCC GTG ACA CTG TAC GGT GGG GAG GTG TAC TGG ACC GAC TGG CGA Phe Ala Val Thr Leu Tyr Gly Glu Val Tyr Trp Thr Asp Trp Arg 1485 1490 1495	4935
ACA AAT ACA CTG GCT AAG GCC AAC AAG TGG ACT GGC CAC AAC GTC ACC Thr Asn Thr Leu Ala Lys Ala Asn Lys Trp Thr Gly His Asn Val Thr 1500 1505 1510	4983
GTG GTA CAG AGG ACC AAC ACC CAG CCC TTC GAC CTG CAG GTG TAT CAC Val Val Gln Arg Thr Asn Thr Gln Pro Phe Asp Leu Gln Val Tyr His 1515 1520 1525 1530	5031
CCT TCC CGG CAG CCC ATG GCT CCA AAC CCA TGT GAG GCC AAT GGC GGC Pro Ser Arg Gln Pro Met Ala Pro Asn Pro Cys Glu Ala Asn Gly Gly 1535 1540 1545	5079
CGG GGC CCC TGT TCC CAT CTG TGC CTC ATC AAC TAC AAC CGG ACC GTC Arg Gly Pro Cys Ser His Leu Cys Leu Ile Asn Tyr Asn Arg Thr Val 1550 1555 1560	5127
TCC TGG GCC TGT CCC CAC CTC ATG AAG CTG CAC AAG GAC AAC ACC ACC Ser Trp Ala Cys Pro His Leu Met Lys Leu His Lys Asp Asn Thr Thr 1565 1570 1575	5175
TGC TAT GAG TTT AAG AAG TTC CTG CTG TAC GCA CGT CAG ATG GAG ATC Cys Tyr Glu Phe Lys Lys Phe Leu Leu Tyr Ala Arg Gln Met Glu Ile 1580 1585 1590	5223
CGG GGC GTG GAC CTG GAT GCC CCG TAC TAC AAT TAT ATC ATC TCC TTC Arg Gly Val Asp Leu Asp Ala Pro Tyr Tyr Asn Tyr Ile Ile Ser Phe 1595 1600 1605 1610	5271
ACG GTG CCT GAT ATC GAC AAT GTC ACG GTG CTG GAC TAT GAT GCC CGA Thr Val Pro Asp Ile Asp Asn Val Thr Val Leu Asp Tyr Asp Ala Arg 1615 1620 1625	5319
GAG CAG CGA GTT TAC TGG TCT GAT GTG CGG ACT CAA GCC ATC AAA AGG Glu Gln Arg Val Tyr Trp Ser Asp Val Arg Thr Gln Ala Ile Lys Arg 1630 1635 1640	5367

FIG. 6a

GCA TTT ATC AAC GGC ACT GGC GTG GAG ACC GTT GTC TCT GCA GAC TTG Ala Phe Ile Asn Gly Thr Gly Val Glu Thr Val Val Ser Ala Asp Leu 1645 1650 1655	5415
CCC AAC GCC CAC GGG CTG GCT GTG GAC TGG GTC TCC CGA AAT CTG TTT Pro Asn Ala His Gly Leu Ala Val Asp Trp Val Ser Arg Asn Leu Phe 1660 1665 1670	5463
TGG ACA AGT TAC GAC ACC AAC AAG AAG CAG ATT AAC GTG GCC CGG CTG Trp Thr Ser Tyr Asp Thr Asn Lys Lys Gln Ile Asn Val Ala Arg Leu 1675 1680 1685 1690	5511
GAC GGC TCC TTC AAG AAT GCG GTG GTG CAG GGC CTG GAG CAG CCC CAC Asp Gly Ser Phe Lys Asn Ala Val Val Gln Gly Leu Glu Gln Pro His 1695 1700 1705	5559
GGC CTG GTC GTC CAC CCG CTT CGT GGC AAG CTC TAC TGG ACT GAT GGG Gly Leu Val Val His Pro Leu Arg Gly Lys Leu Tyr Trp Thr Asp Gly 1710 1715 1720	5607
GAC AAC ATC AGC ATG GCC AAC ATG GAT GGG AGC AAC CAC ACT CTG CTC Asp Asn Ile Ser Met Ala Asn Met Asp Gly Ser Asn His Thr Leu Leu 1725 1730 1735	5655
TTC AGT GGC CAG AAG GGC CCT GTG GGG TTG GCC ATT GAC TTC CCT GAG Phe Ser Gly Gln Lys Gly Pro Val Gly Leu Ala Ile Asp Phe Pro Glu 1740 1745 1750	5703
AGC AAA CTC TAC TGG ATC AGC TCT GGG AAC CAC ACA ATC AAC CGT TGC Ser Lys Leu Tyr Trp Ile Ser Ser Gly Asn His Thr Ile Asn Arg Cys 1755 1760 1765 1770	5751
AAT CTG GAT GGG AGC GAG CTG GAG GTC ATC GAC ACC ATG CGG AGC CAG Asn Leu Asp Gly Ser Glu Leu Glu Val Ile Asp Thr Met Arg Ser Gln 1775 1780 1785	5799
CTG GGC AAG GCC ACT GCC CTG GCC ATC ATG GGG GAC AAG CTG TGG TGG Leu Gly Lys Ala Thr Ala Leu Ala Ile Met Gly Asp Lys Leu Trp Trp 1790 1795 1800	5847
GCA GAT CAG GTG TCA GAG AAG ATG GGC ACG TGC AAC AAA GCC GAT GGC Ala Asp Gln Val Ser Glu Lys Met Gly Thr Cys Asn Lys Ala Asp Gly 1805 1810 1815	5895
TCT GGG TCC GTG GTG CTG CGG AAC AGT ACC ACG TTG GTT ATG CAC ATG Ser Gly Ser Val Val Leu Arg Asn Ser Thr Thr Leu Val Met His Met 1820 1825 1830	5943
AAG GTG TAT GAC GAG AGC ATC CAG CTA GAG CAT GAG GGC ACC AAC CCC Lys Val Tyr Asp Glu Ser Ile Gln Leu Glu His Glu Gly Thr Asn Pro 1835 1840 1845 1850	5991
TGC AGT GTC AAC AAC GGA GAC TGT TCC CAG CTC TGC CTG CCA ACA TCA Cys Ser Val Asn Asn Gly Asp Cys Ser Gln Leu Cys Leu Pro Thr Ser 1855 1860 1865	6039
GAG ACG ACT CGC TCC TGT ATG TGT ACA GCC GGT TAC AGC CTC CGG AGC Glu Thr Thr Arg Ser Cys Met Cys Thr Ala Gly Tyr Ser Leu Arg Ser 1870 1875 1880	6087

FIG. 6a

GGA CAG CAG GCC TGT GAG GGT GTG GGC TCT TTT CTC CTG TAC TCT GTA Gly Gln Gln Ala Cys Glu Gly Val Gly Ser Phe Leu Leu Tyr Ser Val 1885 1890 1895	6135
CAT GAG GGA ATT CGG GGG ATT CCA CTA GAT CCC AAT GAC AAG TCG GAT His Glu Gly Ile Arg Gly Ile Pro Leu Asp Pro Asn Asp Lys Ser Asp 1900 1905 1910	6183
GCC CTG GTC CCA GTG TCC GGA ACT TCA CTG GCT GTC GGA ATC GAC TTC Ala Leu Val Pro Val Ser Gly Thr Ser Leu Ala Val Gly Ile Asp Phe 1915 1920 1925 1930	6231
CAT GCC GAA AAT GAC ACT ATT TAT TGG GTG GAT ATG GGC CTA AGC ACC His Ala Glu Asn Asp Thr Ile Tyr Trp Val Asp Met Gly Leu Ser Thr 1935 1940 1945	6279
ATC AGC AGG GCC AAG CGT GAC CAG ACA TGG CGA GAG GAT GTG GTG ACC Ile Ser Arg Ala Lys Arg Asp Gln Thr Trp Arg Glu Asp Val Val Thr 1950 1955 1960	6327
AAC GGT ATT GGC CGT GTG GAG GGC ATC GCC GTG GAC TGG ATC GCA GGC Asn Gly Ile Gly Arg Val Glu Gly Ile Ala Val Asp Trp Ile Ala Gly 1965 1970 1975	6375
AAC ATA TAC TGG ACG GAC CAG GGC TTC GAT GTC ATC GAG GTT GCC CGG Asn Ile Tyr Trp Thr Asp Gln Gly Phe Asp Val Ile Glu Val Ala Arg 1980 1985 1990	6423
CTC AAT GGC TCT TTT CGT TAT GTG GTC ATT TCC CAG GGT CTG GAC AAG Leu Asn Gly Ser Phe Arg Tyr Val Val Ile Ser Gln Gly Leu Asp Lys 1995 2000 2005 2010	6471
CCT CGG GCC ATC ACT GTC CAC CCA GAG AAG GGG TAC TTG TTC TGG ACC Pro Arg Ala Ile Thr Val His Pro Glu Lys Gly Tyr Leu Phe Trp Thr 2015 2020 2025	6519
GAG TGG GGT CAT TAC CCA CGT ATT GAG CGG TCT CGC CTT GAT GGC ACA Glu Trp Gly His Tyr Pro Arg Ile Glu Arg Ser Arg Leu Asp Gly Thr 2030 2035 2040	6567
GAG AGA GTG GTG TTG GTT AAT GTC AGC ATC AGC TGG CCC AAT GGC ATC Glu Arg Val Val Leu Val Asn Val Ser Ile Ser Trp Pro Asn Gly Ile 2045 2050 2055	6615
TCA GTA GAC TAT CAG GGC GGC AAG CTC TAC TGG TGT GAT GCT CGG ATG Ser Val Asp Tyr Gln Gly Lys Leu Tyr Trp Cys Asp Ala Arg Met 2060 2065 2070	6663
GAC AAG ATC GAG CGC ATC GAC CTG GAA ACG GGC GAG AAC CGG GAG GTG Asp Lys Ile Glu Arg Ile Asp Leu Glu Thr Gly Glu Asn Arg Glu Val 2075 2080 2085 2090	6711
GTC CTG TCC AGC AAT AAC ATG GAT ATG TTC TCC GTG TCC GTG TTT GAG Val Leu Ser Ser Asn Asn Met Asp Met Phe Ser Val Ser Yal Phe Glu 2095 2100 2105	6759
GAC TTC ATC TAC TGG AGT GAC AGA ACT CAC GCC AAT GGC TCC ATC AAG Asp Phe Ile Tyr Trp Ser Asp Arg Thr His Ala Asn Gly Ser Ile Lys 2110 2115 2120	6807

FIG. 6a

CGC GGC TGC AAA GAC AAT GCT ACA GAC TCC GTG CCT CTG AGG ACA GGC Arg Gly Cys Lys Asp Asn Ala Thr Asp Ser Val Pro Leu Arg Thr Gly 2125 2130 2135	6855
ATT GGT GTT CAG CTT AAA GAC ATC AAG GTC TTC AAC AGG GAC AGG CAG Ile Gly Val Gln Leu Lys Asp Ile Lys Val Phe Asn Arg Asp Arg Gln 2140 2145 2150	6903
AAG GGT ACC AAT GTG TGC GCG GTA GCC AAC GGC GGG TGC CAG CAG CTC Lys Gly Thr Asn Val Cys Ala Val Ala Asn Gly Gly Cys Gln Gln Leu 2155 2160 2165 2170	6951
TGC TTG TAT CGG GGT GGC GGA CAG CGA GCC TGT GCC TGT GCC CAC GGG Cys Leu Tyr Arg Gly Gly Gln Arg Ala Cys Ala Cys Ala His Gly 2175 2180 2185	6999
ATG CTG GCA GAA GAC GGG GCC TCA TGC CGA GAG TAC GCT GGC TAC CTG Met Leu Ala Glu Asp Gly Ala Ser Cys Arg Glu Tyr Ala Gly Tyr Leu 2190 2195 2200	7047
CTC TAC TCA GAG CGG ACC ATC CTC AAG AGC ATC CAC CTG TCG GAT GAG Leu Tyr Ser Glu Arg Thr Ile Leu Lys Ser Ile His Leu Ser Asp Glu 2205 2210 2215	7095
CGT AAC CTC AAC GCA CCG GTG CAG CCC TTT GAA GAC CCC GAG CAC ATG Arg Asn Leu Asn Ala Pro Val Gln Pro Phe Glu Asp Pro Glu His Met 2220 2225 2230	7143
AAA AAT GTC ATC GCC CTG GCC TTT GAC TAC CGA GCA GGC ACC TCC CCG Lys Asn Val Ile Ala Leu Ala Phe Asp Tyr Arg Ala Gly Thr Ser Pro 2235 2240 2245 2250	7191
GGG ACC CCT AAC CGC ATC TTC TTC AGT GAC ATC CAC TTT GGG AAC ATC Gly Thr Pro Asn Arg Ile Phe Phe Ser Asp Ile His Phe Gly Asn Ile 2255 2260 2265	7239
CAG CAG ATC AAT GAC GAT GGC TCG GGC AGG ACC ACC ATC GTG GAA AAT Gln Gln Ile Asn Asp Asp Gly Ser Gly Arg Thr Thr Ile Val Glu Asn 2270 2275 2280	7287
GTG GGC TCT GTG GAA GGC CTG GCC TAT CAC CGT GGC TGG GAC ACA CTG Val Gly Ser Val Glu Gly Leu Ala Tyr His Arg Gly Trp Asp Thr Leu 2285 2290 2295	7335
TAC TGG ACA AGC TAC ACC ACA TCC ACC ATC ACC CGC CAC ACC GTG GAC Tyr Trp Thr Ser Tyr Thr Ser Thr Ile Thr Arg His Thr Val Asp 2300 2305 2310	7383
CAG ACT CGC CCA GGG GCC TTC GAG AGG GAG ACA GTC ATC ACC ATG TCC Gln Thr Arg Pro Gly Ala Phe Glu Arg Glu Thr Val Ile Thr Met Ser 2315 2320 2325 2330	7431
GGA GAC GAC CAC CCG AGA GCC TTT GTG CTG GAT GAG TGC CAG AAC CTG Gly Asp Asp His Pro Arg Ala Phe Val Leu Asp Glu Cys Gln Asn Leu 2335 2340 2345	7479
ATG TTC TGG ACC AAT TGG AAC GAG CTC CAT CCA AGC ATC ATG CGG GCA Met Phe Trp Thr Asn Trp Asn Glu Leu His Pro Ser Ile Met Arg Ala 2350 2355 2360	7527

FIG. 6a

GCC CTA TCC GGA GCC AAC GTC CTG ACC CTC ATT GAG AAG GAC ATC CGC Ala Leu Ser Gly Ala Asn Val Leu Thr Leu Ile Glu Lys Asp Ile Arg 2365 2370 2375	7575
ACG CCC AAT GGG TTG GCC ATC GAC CAC CGG GCG GAG AAG CTG TAC TTC Thr Pro Asn Gly Leu Ala Ile Asp His Arg Ala Glu Lys Leu Tyr Phe 2380 2385 2390	7623
TCG GAT GCC ACC TTG GAC AAG ATC GAG CGC TGC GAG TAC GAC GGC TCC Ser Asp Ala Thr Leu Asp Lys Ile Glu Arg Cys Glu Tyr Asp Gly Ser 2395 2400 2405 2410	7671
CAC CGC TAT GTG ATC CTA AAG TCG GAG CCC GTC CAC CCC TTT GGG TTG His Arg Tyr Val Ile Leu Lys Ser Glu Pro Val His Pro Phe Gly Leu 2415 2420 2425	7719
GCG GTG TAC GGA GAG CAC ATT TTC TGG ACT GAC TGG GTG CGG CGG GCT Ala Val Tyr Gly Glu His Ile Phe Trp Thr Asp Trp Val Arg Arg Ala 2430 2435 2440	7767
GTG CAG CGA GCC AAC AAG TAT GTG GGC AGC GAC ATG AAG CTG CTT CGG Val Gln Arg Ala Asn Lys Tyr Val Gly Ser Asp Met Lys Leu Leu Arg 2445 2450 2455	7815
GTG GAC ATT CCC CAG CAA CCC ATG GGC ATC ATC GCC GTG GCC AAT GAC Val Asp Ile Pro Gln Gln Pro Met Gly Ile Ile Ala Val Ala Asn Asp 2460 2465 2470	7863
ACC AAC AGC TGT GAA CTC TCC CCC TGC CGT ATC AAC AAT GGA GGC TGC Thr Asn Ser Cys Glu Leu Ser Pro Cys Arg Ile Asn Asn Gly Gly Cys 2475 2480 2485 2490	7911
CAG GAT CTG TGT CTG CTC ACC CAC CAA GGC CAC GTC AAC TGT TCC TGT Gln Asp Leu Cys Leu Leu Thr His Gln Gly His Val Asn Cys Ser Cys 2495 2500 2505	7959
CGA GGG GGC CGG ATC CTC CAG GAG GAC TTC ACC TGC CGG GCT GTG AAC Arg Gly Arg Ile Leu Gln Glu Asp Phe Thr Cys Arg Ala Val Asn 2510 2515 2520	8007
TCC TCT TGT CGG GCA CAA GAT GAG TTT GAG TGT GTC AAT GGG GAA TGT Ser Ser Cys Arg Ala Gln Asp Glu Phe Glu Cys Ala Asn Gly Glu Cys 2525 2530 2535	8055
ATC AGC TTC AGC CTC ACC TGT GAT GGC GTC TCC CAC TGC AAG GAC AAG Ile Ser Phe Ser Leu Thr Cys Asp Gly Val Ser His Cys Lys Asp Lys 2540 2545 2550	8103
TCC GAT GAG AAG CCC TCC TAC TGC AAC TCA CGC CGC TGC AAG AAG ACT Ser Asp Glu Lys Pro Ser Tyr Cys Asn Ser Arg Arg Cys Lys Lys Thr 2555 2560 2565 2570	8151
TTC CGC CAG TGT AAC AAT GGC CGC TGT GTA TCC AAC ATG CTG TGG TGC Phe Arg Gln Cys Asn Asn Gly Arg Cys Val Ser Asn Met Leu Trp Cys 2575 2580 2585	8199
AAT GGG GTG GAT TAC TGT GGG GAT GGC TCT GAT GAG ATA CCT TGC AAC Asn Gly Val Asp Tyr Cys Gly Asp Gly Ser Asp Glu Ile Pro Cys Asn 2590 2595 2600	8247

FIG. 6a

AAG ACT GCC TGT GGT GTG GGT GAG TTC CGC TGC CGG GAT GGG TCC TGC Lys Thr Ala Cys Gly Val Gly Glu Phe Arg Cys Arg Asp Gly Ser Cys 2605 2610 2615	8295
ATC GGG AAC TCC AGT CGC TGC AAC CAG TTT GTG GAT TGT GAG GAT GCC Ile Gly Asn Ser Ser Arg Cys Asn Gln Phe Val Asp Cys Glu Asp Ala 2620 2625 2630	8343
TCG GAT GAG ATG AAT TGC AGT GCC ACA GAC TGC AGC AGC TAT TTC CGC Ser Asp Glu Met Asn Cys Ser Ala Thr Asp Cys Ser Ser Tyr Phe Arg 2635 2640 2645 2650	8391
CTG GGC GTG AAA GGT GTC CTC TTC CAG CCG TGC GAG CGG ACA TCC CTG Leu Gly Val Lys Gly Val Leu Phe Gln Pro Cys Glu Arg Thr Ser Leu 2655 2660 2665	8439
TGC TAC GCA CCT AGC TGG GTG TGT GAT GGC GCC AAC GAC TGT GGA GAC Cys Tyr Ala Pro Ser Trp Val Cys Asp Gly Ala Asn Asp Cys Gly Asp 2670 2675 2680	8487
TAC AGC GAT GAA CGT GAC TGT CCA GGT GTG AAG CGC CCT AGG TGC CCG Tyr Ser Asp Glu Arg Asp Cys Pro Gly Val Lys Arg Pro Arg Cys Pro 2685 2690 2695	8535
CTC AAT TAC TTT GCC TGC CCC AGC GGG CGC TGT ATC CCC ATG AGC TGG Leu Asn Tyr Phe Ala Cys Pro Ser Gly Arg Cys Ile Pro Met Ser Trp 2700 2705 2710	8583
ACG TGT GAC AAG GAG GAT GAC TGT GAG AAC GGC GAG GAT GAG ACC CAC Thr Cys Asp Lys Glu Asp Asp Cys Glu Asn Gly Glu Asp Glu Thr His 2715 2720 2725 2730	8631
TGC AAC AAG TTC TGC TCA GAG GCA CAG TTC GAG TGC CAG AAC CAC CGG Cys Asn Lys Phe Cys Ser Glu Ala Gln Phe Glu Cys Gln Asn His Arg 2735 2740 2745	8679
TGT ATC TCC AAG CAG TGG CTG TGT GAC GGT AGC GAT GAT TGC GGG GAT Cys Ile Ser Lys Gln Trp Leu Cys Asp Gly Ser Asp Asp Cys Gly Asp 2750 2755 2760	8727
GGC TCC GAT GAG GCA GCT CAC TGT GAA GGC AAG ACA TGT GGC CCC TCC Gly Ser Asp Glu Ala Ala His Cys Glu Gly Lys Thr Cys Gly Pro Ser 2765 2770 2775	8775
TCC TTC TCC TGT CCC GGC ACC CAC GTG TGT GTC CCT GAG CGC TGG CTC Ser Phe Ser Cys Pro Gly Thr His Val Cys Val Pro Glu Arg Trp Leu 2780 2785 2790	8823
TGT GAT GGC GAC AAG GAC TGT ACC GAT GGC GCG GAT GAG AGT GTC ACT Cys Asp Gly Asp Lys Asp Cys Thr Asp Gly Ala Asp Glu Ser Val Thr 2795 2800 2805 2810	8871
GCT GGC TGC CTG TAC AAC AGC ACC TGT GAT GAC CGT GAG TTC ATG TGC Ala Gly Cys Leu Tyr Asn Ser Thr Cys Asp Asp Arg Glu Phe Met Cys 2815 2820 2825	8919
CAG AAC CGC TTG TGT ATT CCC AAG CAT TTC GTG TGC GAC CAT GAC CGT Gln Asn Arg Leu Cys Ile Pro Lys His Phe Val Cys Asp His Asp Arg 2830 2835 2840	8967

FIG. 6a

GAC TGT GCT GAT GGC TCT GAT GAA TCC CCT GAG TGT GAG TAC CCA ACC Asp Cys Ala Asp Gly Ser Asp Glu Ser Pro Glu Cys Glu Tyr Pro Thr 2845 2850 2855	9015
TGC GGG CCC AAT GAA TTC CGC TGT GCC AAT GGG CGT TGT CTG AGC TCC Cys Gly Pro Asn Glu Phe Arg Cys Ala Asn Gly Arg Cys Leu Ser Ser 2860 2865 2870	9063
CGT CAG TGG GAA TGT GAT GGG GAG AAT GAC TGT CAC GAC CAC AGC GAT Arg Gln Trp Glu Cys Asp Gly Glu Asn Asp Cys His Asp His Ser Asp 2875 2880 2885 2890	9111
GAG GCT CCC AAG AAC CCA CAC TGC ACC AGC CCA GAG CAC AAA TGC AAT Glu Ala Pro Lys Asn Pro His Cys Thr Ser Pro Glu His Lys Cys Asn 2895 2900 2905	9159
GCC TCA TCA CAG TTC CTG TGC AGC AGC GGG CGC TGC GTG GCT GAG GCG Ala Ser Ser Gln Phe Leu Cys Ser Ser Gly Arg Cys Val Ala Glu Ala 2910 2915 2920	9207
TTG CTC TGC AAC GGC CAG GAC GAC TGT GGG GAC GGT TCA GAC GAA CGC Leu Leu Cys Asn Gly Gln Asp Asp Cys Gly Asp Gly Ser Asp Glu Arg 2925 2930 2935	9255
GGG TGC CAT GTC AAC GAG TGT CTC AGC CGC AAG CTC AGT GGC TGC AGT Gly Cys His Val Asn Glu Cys Leu Ser Arg Lys Leu Ser Gly Cys Ser 2940 2945 2950	9303
CAG GAC TGC GAG GAC CTC AAG ATA GGC TTT AAG TGC CGC TGT CGC CCG Gln Asp Cys Glu Asp Leu Lys Ile Gly Phe Lys Cys Arg Cys Arg Pro 2955 2960 2965 2970	9351
GGC TTC CGG CTA AAG GAC GAT GGC AGG ACC TGT GCC GAC CTG GAT GAG Gly Phe Arg Leu Lys Asp Asp Gly Arg Thr Cys Ala Asp Leu Asp Glu 2975 2980 2985	9399
TGC AGC ACC ACC TTC CCC TGC AGC CAG CTC TGC ATC AAC ACC CAC GGA Cys Ser Thr Thr Phe Pro Cys Ser Gln Leu Cys Ile Asn Thr His Gly 2990 2995 3000	9447
AGT TAC AAG TGT CTG TGT GTG GAG GGC TAT GCA CCC CGT GGC GGT GAC Ser Tyr Lys Cys Leu Cys Val Glu Gly Tyr Ala Pro Arg Gly Gly Asp 3005 3010 3015	9495
CCC CAC AGC TGC AAA GCT GTG ACC GAT GAG GAG CCA TTT CTC ATC TTT Pro His Ser Cys Lys Ala Val Thr Asp Glu Glu Pro Phe Leu Ile Phe 3020 3025 3030	9543
GCC AAC CGG TAC TAC CTG CGG AAG CTC AAC CTG GAC GGC TCC AAC TAC Ala Asn Arg Tyr Tyr Leu Arg Lys Leu Asn Leu Asp Gly Ser Asn Tyr 3035 3040 3045 3050	9591
ACA CTG CTT AAG CAG GGC CTG AAC AAT GCG GTC GCC TTG GCA TTT GAC Thr Leu Leu Lys Gln Gly Leu Asn Asn Ala Val Ala Leu Ala Phe Asp 3055 3060 3065	9639
TAC CGA GAG CAG ATG ATC TAC TGG ACG GGC GTG ACC ACC CAG GGC AGC Tyr Arg Glu Gln Met Ile Tyr Trp Thr Gly Val Thr Thr Gln Gly Ser 3070 3075 3080	9687

FIG. 6a

ATG ATT CGC AGG ATG CAC CTC AAC GGC AGC AAC GTG CAG GTT CTG CAC Met Ile Arg Arg Met His Leu Asn Gly Ser Asn Val Gln Val Leu His 3085 3090 3095	9735
CGG ACG GGC CTT AGT AAC CCA GAT GGG CTC GCT GTG GAC TGG GTG GGT Arg Thr Gly Leu Ser Asn Pro Asp Gly Leu Ala Val Asp Trp Val Gly 3100 3105 3110	9783
GGC AAC CTG TAC TGG TGT GAC AAG GGC AGA GAT ACC ATT GAG GTG TCC Gly Asn Leu Tyr Trp Cys Asp Lys Gly Arg Asp Thr Ile Glu Val Ser 3115 3120 3125 3130	9831
AAG CTT AAC GGG GCC TAT CGG ACA GTG CTG GTC AGC TCT GGC CTC CGG Lys Leu Asn Gly Ala Tyr Arg Thr Val Leu Val Ser Ser Gly Leu Arg 3135 3140 3145	9879
GAG CCC AGA GCT CTG GTA GTG GAT GTA CAG AAT GGG TAC CTG TAC TGG Glu Pro Arg Ala Leu Val Val Asp Val Gln Asn Gly Tyr Leu Tyr Trp 3150 3155 3160	9927
ACA GAC TGG GGT GAC CAC TCA CTG ATC GGC CGG ATT GGC ATG GAT GGA Thr Asp Trp Gly Asp His Ser Leu Ile Gly Arg Ile Gly Met Asp Gly 3165 3170 3175	9975
TCT GGC CGC AGC ATC ATC GTG GAC ACT AAG ATC ACA TGG CCC AAT GGC Ser Gly Arg Ser Ile Ile Val Asp Thr Lys Ile Thr Trp Pro Asn Gly 3180 3185 3190	10023
CTG ACC GTG GAC TAC GTC ACG GAA CGC ATC TAC TGG GCT GAC GCC CGT Leu Thr Val Asp Tyr Val Thr Glu Arg Ile Tyr Trp Ala Asp Ala Arg 3195 3200 3205 3210	10071
GAG GAC TAC ATC GAG TTC GCC AGC CTG GAT GGC TCC AAC CGT CAC GTT Glu Asp Tyr Ile Glu Phe Ala Ser Leu Asp Gly Ser Asn Arg His Val 3215 3220 3225	10119
GTG CTG AGC CAA GAC ATC CCA CAC ATC TTT GCG CTG ACC CTA TTT GAA Val Leu Ser Gln Asp Ile Pro His Ile Phe Ala Leu Thr Leu Phe Glu 3230 3235 3240	10167
GAC TAC GTC TAC TGG ACA GAC TGG GAA ACG AAG TCC ATC AAC CGG GCC Asp Tyr Val Tyr Trp Thr Asp Trp Glu Thr Lys Ser Ile Asn Arg Ala 3245 3250 3255	10215
CAC AAG ACC ACG GGT GCC AAC AAA ACA CTC CTC ATC AGC ACC CTG CAC His Lys Thr Thr Gly Ala Asn Lys Thr Leu Leu Ile Ser Thr Leu His 3260 3265 3270	10263
CGG CCC ATG GAC TTA CAT GTA TTC CAC GCC CTG CGC CAG CCA GAT GTG Arg Pro Met Asp Leu His Val Phe His Ala Leu Arg Gln Pro Asp Val 3275 3280 3285 3290	10311
CCC AAT CAC CCC TGC AAA GTC AAC AAT GGT GGC TGC AGC AAC CTG TGC Pro Asn His Pro Cys Lys Val Asn Asn Gly Gly Cys Ser Asn Leu Cys 3295 3300 3305	10359
CTG CTG TCC CCT GGG GGT GGT CAC AAG TGC GCC TGC CCC ACC AAC TTC Leu Leu Ser Pro Gly Gly His Lys Cys Ala Cys Pro Thr Asn Phe 3310 3315 3320	10407

FIG. 6a

TAT CTG GGT GGC GAT GGC CGT ACC TGT GTG TCC AAC TGC ACA GCA AGC Tyr Leu Gly Gly Asp Gly Arg Thr Cys Val Ser Asn Cys Thr Ala Ser 3325 3330 3335	10455
CAG TTT GTG TGC AAA AAT GAC AAG TGC ATC CCC TTC TGG TGG AAG TGT Gln Phe Val Cys Lys Asn Asp Lys Cys Ile Pro Phe Trp Trp Lys Cys 3340 3345 3350	10503
GAC ACG GAG GAC GAC TGT GGG GAT CAC TCA GAC GAG CCT CCA GAC TGT Asp Thr Glu Asp Asp Cys Gly Asp His Ser Asp Glu Pro Pro Asp Cys 3355 3360 3365 3370	10551
CCC GAG TTC AAG TGC CGC CCA GGC CAG TTC CAG TGC TCC ACC GGC ATC Pro Glu Phe Lys Cys Arg Pro Gly Gln Phe Gln Cys Ser Thr Gly Ile 3375 3380 3385	10599
TGC ACC AAC CCT GCC TTC ATC TGT GAT GGG GAC AAT GAC TGC CAA GAC Cys Thr Asn Pro Ala Phe Ile Cys Asp Gly Asp Asn Asp Cys Gln Asp 3390 3395 3400	10647
AAT AGT GAC GAG GCC AAT TGC GAC ATT CAC GTC TGC TTG CCC AGC CAA Asn Ser Asp Glu Ala Asn Cys Asp Ile His Val Cys Leu Pro Ser Gln 3405 3410 3415	10695
TTC AAG TGC ACC AAC ACC AAC CGC TGC ATT CCT GGC ATC TTC CGT TGC Phe Lys Cys Thr Asn Thr Asn Arg Cys Ile Pro Gly Ile Phe Arg Cys 3420 3425 3430	10743
AAT GGG CAG GAC AAC TGC GGG GAC GGC GAG GAT GAG CGG GAT TGC CCT Asn Gly Gln Asp Asn Cys Gly Asp Gly Glu Asp Glu Arg Asp Cys Pro 3435 3440 3445 3450	10791
GAG GTG ACC TGC GCC CCC AAC CAG TTC CAG TGC TCC ATC ACC AAG CGC Glu Val Thr Cys Ala Pro Asn Gln Phe Gln Cys Ser Ile Thr Lys Arg 3455 3460 3465	10839
TGC ATC CCT CGC GTC TGG GTC TGT GAC AGG GAT AAT CAC TGT GTG GAC Cys Ile Pro Arg Val Trp Val Cys Asp Arg Asp Asn His Cys Val Asp 3470 3475 3480	10887
GGC AGT GAT GAG CCT GCC AAC TGT ACC CAA ATG ACC TGT GGA GTG GAT Gly Ser Asp Glu Pro Ala Asn Cys Thr Gln Met Thr Cys Gly Val Asp 3485 3490 3495	10935
GAG TTC CGC TGC AAG GAT TCT GGC CGC TGC ATC CCC GCG CGC TGG AAG Glu Phe Arg Cys Lys Asp Ser Gly Arg Cys Ile Pro Ala Arg Trp Lys 3500 3505 3510	10983
TGT GAC GGA GAA GAT GAC TGT GGG GAT GGT TCA GAT GAG CCC AAG GAA Cys Asp Gly Glu Asp Asp Cys Gly Asp Gly Ser Asp Glu Pro Lys Glu 3515 3520 3525 3530	11031
GAG TGT GAT GAG CGC ACC TGT GAG CCA TAC CAG TTC CGC TGC AAA AAC Glu Cys Asp Glu Arg Thr Cys Glu Pro Tyr Gln Phe Arg Cys Lys Asn 3535 3540 3545	11079
AAC CGC TGT GTC CCA GGC CGT TGG CAA TGT GAC TAC GAC AAC GAC TGC Asn Arg Cys Val Pro Gly Arg Trp Gln Cys Asp Tyr Asn Asp Cys 3550 3555 3560	11127

FIG. 6a

GGA GAT AAC TCG GAC GAG GAG AGC TGC ACA CCT CGG CCC TGC TCT GAG		11175
Gly Asp Asn Ser Asp Glu Glu Ser Cys Thr Pro Arg Pro Cys Ser Glu		
3565 3570 3575		
AGT GAG TTT TTC TGT GCC AAT GGC CGC TGC ATC GCT GGG CGC TGG AAG		11223
Ser Glu Phe Phe Cys Ala Asn Gly Arg Cys Ile Ala Gly Arg Trp Lys		
3580 3585 3590		
TGT GAT GGG GAC CAT GAC TGT GCC GAC GGC TCA GAC GAG AAA GAC TGC		11271
Cys Asp Gly Asp His Asp Cys Ala Asp Gly Ser Asp Glu Lys Asp Cys		
3595 3600 3605 3610		
ACC CCC CGC TGT GAT ATG GAC CAG TTC CAG TGC AAG AGT GGC CAC TGC		11319
Thr Pro Arg Cys Asp Met Asp Gln Phe Gln Cys Lys Ser Gly His Cys		
3615 3620 3625		
ATC CCC CTG CGC TGG CCG TGT GAC GCG GAT GCT GAC TGT ATG GAC GGC		11367
Ile Pro Leu Arg Trp Pro Cys Asp Ala Asp Ala Asp Cys Met Asp Gly		
3630 3635 3640		
AGT GAC GAG GAA GCC TGT GGC ACT GGG GTG AGG ACC TGC CCA TTG GAT		11415
Ser Asp Glu Glu Ala Cys Gly Thr Gly Val Arg Thr Cys Pro Leu Asp		
3645 3650 3655		
GAG TTT CAA TGT AAC AAC ACC TTG TGC AAG CCG CTG GCC TGG AAG TGT		11463
Glu Phe Gln Cys Asn Asn Thr Leu Cys Lys Pro Leu Ala Trp Lys Cys		
3660 3665 3670		
GAT GGA GAG GAC GAC TGT GGG GAC AAC TCA GAT GAG AAC CCC GAG GAA		11511
Asp Gly Glu Asp Asp Cys Gly Asp Asn Ser Asp Glu Asn Pro Glu Glu		
3675 3680 3685 3690		
TGC GCC CGG TTC ATC TGC CCT CCC AAC CGG CCT TTC CGC TGC AAG AAT		11559
Cys Ala Arg Phe Ile Cys Pro Pro Asn Arg Pro Phe Arg Cys Lys Asn		
3695 3700 3705		
GAC CGA GTC CTG TGG ATT GGG CGC CAG TGT GAT GGC GTG GAC AAC		11607
Asp Arg Val Cys Leu Trp Ile Gly Arg Gln Cys Asp Gly Val Asp Asn		
3710 3715 3720		
TGT GGA GAT GGG ACT GAC GAG GAG GAC TGT GAG CCC CCC ACG GCC CAG		11655
Cys Gly Asp Gly Thr Asp Glu Glu Asp Cys Glu Pro Pro Thr Ala Gln		
3725 3730 3735		
AAC CCC CAC TGC AAA GAC AAG AAG GAG TTC CTG TGC CGA AAC CAG CGC		11703
Asn Pro His Cys Lys Asp Lys Lys Glu Phe Leu Cys Arg Asn Gln Arg		
3740 3745 3750		
TGT CTA TCA TCC TCC CTG CGC TGT AAC ATG TTC GAT GAC TGC GGC GAT		11751
Cys Leu Ser Ser Leu Arg Cys Asn Met Phe Asp Asp Cys Gly Asp		
3755 3760 3765 3770		
GGC TCC GAT GAA GAA GAT TGC AGC ATC GAC CCC AAG CTG ACC AGC TGT		11799
Gly Ser Asp Glu Glu Asp Cys Ser Ile Asp Pro Lys Leu Thr Ser Cys		
3775 3780 3785		
GCC ACC AAT GCC AGC ATG TGT GGG GAC GAA GCT CGT TGT GTG CGC ACT		11847
Ala Thr Asn Ala Ser Met Cys Gly Asp Glu Ala Arg Cys Val Arg Thr		
3790 3795 3800		

GAG AAA GCT GCC TAC TGT GCC TGC CGC TCG GGC TTC CAT ACT GTG CCG Glu Lys Ala Ala Tyr Cys Ala Cys Arg Ser Gly Phe His Thr Val Pro 3805 3810 3815	11895
GGC CAG CCC GGA TGC CAG GAC ATC AAC GAG TGC CTG CGC TTT GGT ACC Gly Gln Pro Gly Cys Gln Asp Ile Asn Glu Cys Leu Arg Phe Gly Thr 3820 3825 3830	11943
TGC TCT CAG CTC TGG AAC AAA CCC AAG GGA GGC CAC CTC TGC AGC TGT Cys Ser Gln Leu Trp Asn Lys Pro Lys Gly His Leu Cys Ser Cys 3835 3840 3845 3850	11991
GCC CGC AAC TTC ATG AAG ACA CAC AAC ACC TGC AAA GCT GAA GGC TCC Ala Arg Asn Phe Met Lys Thr His Asn Thr Cys Lys Ala Glu Gly Ser 3855 3860 3865	12039
GAG TAC CAG GTG CTA TAC ATC GCG GAT GAC AAC GAG ATC CGC AGC TTG Glu Tyr Gln Val Leu Tyr Ile Ala Asp Asp Asn Glu Ile Arg Ser Leu 3870 3875 3880	12087
TTC CCG GGC CAC CCC CAC TCA GCC TAC GAG CAG ACA TTC CAG GGC GAT Phe Pro Gly His Pro His Ser Ala Tyr Glu Gln Thr Phe Gln Gly Asp 3885 3890 3895	12135
GAG AGT GTC CGC ATA GAT GCC ATG GAT GTC CAT GTC AAG GCC GGC CGT Glu Ser Val Arg Ile Asp Ala Met Asp Val His Val Lys Ala Gly Arg 3900 3905 3910	12183
GTC TAC TGG ACT AAC TGG CAC ACG GGC ACA ATC TCC TAC AGG AGC CTG Val Tyr Trp Thr Asn Trp His Thr Gly Thr Ile Ser Tyr Arg Ser Leu 3915 3920 3925 3930	12231
CCC CCT GCC GCC CCT CCT ACC ACT TCC AAC CGC CAC CGG AGG CAG ATC Pro Pro Ala Ala Pro Pro Thr Thr Ser Asn Arg His Arg Arg Gln Ile 3935 3940 3945	12279
GAC CGG GGT GTC ACC CAC CTC AAT ATT TCA GGG CTG AAG ATG CCG AGG Asp Arg Gly Val Thr His Leu Asn Ile Ser Gly Leu Lys Met Pro Arg 3950 3955 3960	12327
GGT ATC GCT ATC GAC TGG GTG GCC GGG AAT GTG TAC TGG ACC GAT TCC Gly Ile Ala Ile Asp Trp Val Ala Gly Asn Val Tyr Trp Thr Asp Ser 3965 3970 3975	12375
GGC CGA GAC GTG ATT GAG GTG GCG CAA ATG AAG GGC GAG AAC CGC AAG Gly Arg Asp Val Ile Glu Val Ala Gln Met Lys Gly Glu Asn Arg Lys 3980 3985 3990	12423
ACG CTC ATC TCG GGC ATG ATT GAT GAG CCC CAT GCC ATC GTG GTG GAC Thr Leu Ile Ser Gly Met Ile Asp Glu Pro His Ala Ile Val Val Asp 3995 4000 4005 4010	12471
CCT CTG AGG GGC ACC ATG TAC TGG TCA GAC TGG GGG AAC CAC CCC AAG Pro Leu Arg Gly Thr Met Tyr Trp Ser Asp Trp Gly Asn His Pro Lys 4015 4020 4025	12519
ATT GAA ACA GCA GCG ATG GAT GGC ACC CTT CGG GAG ACT CTC GTG CAA Ile Glu Thr Ala Ala Met Asp Gly Thr Leu Arg Glu Thr Leu Val Gln 4030 4035 4040	12567

GAC AAC ATT CAG TGG CCT ACA GGG CTG GCT GTG GAC TAT CAC AAT GAA Asp Asn Ile Gln Trp Pro Thr Gly Leu Ala Val Asp Tyr His Asn Glu 4045 4050 4055	12615
CGG CTC TAC TGG GCA GAT GCC AAG CTT TCG GTC ATC GGC AGC ATC CGG Arg Leu Tyr Trp Ala Asp Ala Lys Leu Ser Val Ile Gly Ser Ile Arg 4060 4065 4070	12663
CTC AAC GGC ACT GAC CCC ATT GTG GCT GAC AGC AAA CGA GGC CTA Leu Asn Gly Thr Asp Pro Ile Val Ala Ala Asp Ser Lys Arg Gly Leu 4075 4080 4085 4090	12711
AGT CAC CCC TTC AGC ATC GAT GTG TTT GAA GAC TAC ATC TAC GGA GTC Ser His Pro Phe Ser Ile Asp Val Phe Glu Asp Tyr Ile Tyr Gly Val 4095 4100 4105	12759
ACT TAC ATC AAT AAT CGT GTC TTC AAG ATC CAC AAG TTT GGA CAC AGC Thr Tyr Ile Asn Asn Arg Val Phe Lys Ile His Lys Phe Gly His Ser 4110 4115 4120	12807
CCC TTG TAC AAC CTA ACT GGG GGC CTG AGC CAT GCC TCT GAT GTA GTC Pro Leu Tyr Asn Leu Thr Gly Gly Leu Ser His Ala Ser Asp Val Val 4125 4130 4135	12855
CTT TAC CAT CAA CAC AAG CAG CCT GAA GTG ACC AAC CCC TGT GAC CGC Leu Tyr His Gln His Lys Gln Pro Glu Val Thr Asn Pro Cys Asp Arg 4140 4145 4150	12903
AAG AAA TGC GAA TGG CTG TGT CTG AGC CCC AGC GGG CCT GTC TGC Lys Lys Cys Glu Trp Leu Cys Leu Leu Ser Pro Ser Gly Pro Val Cys 4155 4160 4165 4170	12951
ACC TGT CCC AAT GGA AAG AGG CTG GAT AAT GGC ACC TGT GTG CCT GTG Thr Cys Pro Asn Gly Lys Arg Leu Asp Asn Gly Thr Cys Val Pro Val 4175 4180 4185	12999
CCC TCT CCA ACA CCC CCT CCA GAT GCC CCT AGG CCT GGA ACC TGC ACT Pro Ser Pro Thr Pro Pro Asp Ala Pro Arg Pro Gly Thr Cys Thr 4190 4195 4200	13047
CTG CAG TGC TTC AAT GGT GGT AGT TGT TTC CTC AAC GCT CGG AGG CAG Leu Gln Cys Phe Asn Gly Gly Ser Cys Phe Leu Asn Ala Arg Arg Gln 4205 4210 4215	13095
CCC AAG TGC CGT TGC CAG CCC CGT TAC ACA GGC GAT AAG TGT GAG CTG Pro Lys Cys Arg Cys Gln Pro Arg Tyr Thr Gly Asp Lys Cys Glu Leu 4220 4225 4230	13143
GAT CAG TGC TGG GAA TAC TGT CAC AAC GGA GGC ACC TGT GCG GCT TCC Asp Gln Cys Trp Glu Tyr Cys His Asn Gly Gly Thr Cys Ala Ala Ser 4235 4240 4245 4250	13191
CCA TCT GGC ATG CCC ACG TGC CGC TGT CCC ACT GGC TTC ACG GGC CCC Pro Ser Gly Met Pro Thr Cys Arg Cys Pro Thr Gly Phe Thr Gly Pro 4255 4260 4265	13239
AAA TGC ACC GCA CAG GTG TGT GCA GGC TAC TGC TCT AAC AAC AGC ACC Lys Cys Thr Ala Gln Val Cys Ala Gly Tyr Cys Ser Asn Asn Ser Thr 4270 4275 4280	13287

FIG. 6a

TGC ACC GTC AAC CAG GGC AAC CAG CCC CAG TGC CGA TGT CTA CCT GGC	13335
Cys Thr Val Asn Gln Gly Asn Gln Pro Gln Cys Arg Cys Leu Pro Gly	
4285 4290 4295	
TTC CTG GGC GAC CGT TGC CAG TAC CGG CAG TGC TCT GGC TTC TGT GAG	13383
Phe Leu Gly Asp Arg Cys Gln Tyr Arg Gln Cys Ser Gly Phe Cys Glu	
4300 4305 4310	
AAC TTT GGC ACC TGT CAG ATG GCT GAT GGC TCC CGA CAA TGT CGC	13431
Asn Phe Gly Thr Cys Gln Met Ala Ala Asp Gly Ser Arg Gln Cys Arg	
4315 4320 4325 4330	
TGC ACC GTC TAC TTT GAG GGA CCA AGG TGT GAG GTG AAC AAG TGT AGT	13479
Cys Thr Val Tyr Phe Glu Gly Pro Arg Cys Glu Val Asn Lys Cys Ser	
4335 4340 4345	
CGC TGT CTC CAA GGC GCC TGT GTG GTC AAT AAG CAG ACC GGA GAT GTC	13527
Arg Cys Leu Gln Gly Ala Cys Val Val Asn Lys Gln Thr Gly Asp Val	
4350 4355 4360	
ACA TGC AAC TGC ACT GAT GGC CGG GTA GCC CCC AGT TGT CTC ACC TGC	13575
Thr Cys Asn Cys Thr Asp Gly Arg Val Ala Pro Ser Cys Leu Thr Cys	
4365 4370 4375	
ATC GAT CAC TGT AGC AAT GGT GGC TCC TGC ACC ATG AAC AGC AAG ATG	13623
Ile Asp His Cys Ser Asn Gly Gly Ser Cys Thr Met Asn Ser Lys Met	
4380 4385 4390	
ATG CCT GAG TGC CAG TGC CCG CCC CAT ATG ACA GGA CCC CGG TGC CAG	13671
Met Pro Glu Cys Gln Cys Pro Pro His Met Thr Gly Pro Arg Cys Gln	
4395 4400 4405 4410	
GAG CAG GTT AGT CAG CAA CAG CCT GGG CAT ATG GCC TCC ATC CTG	13719
Glu Gln Val Val Ser Gln Gln Pro Gly His Met Ala Ser Ile Leu	
4415 4420 4425	
ATC CCT CTG CTG CTT CTC CTG CTG CTT CTG GTG GCT GGC GTG GTG	13767
Ile Pro Leu Leu Leu Leu Leu Leu Val Ala Gly Val Val	
4430 4435 4440 4445	
TTC TGG TAT AAG CGG CGA GTC CGA GGG GCT AAG GGC TTC CAG CAC CAG	13815
Phe Trp Tyr Lys Arg Arg Val Arg Gly Ala Lys Gly Phe Gln His Gln	
4445 4450 4455	
CGG ATG ACC AAT GGG GCC ATG AAT GTG GAA ATT GGA AAC CCT ACC TAC	13863
Arg Met Thr Asn Gly Ala Met Asn Val Glu Ile Gly Asn Pro Thr Tyr	
4460 4465 4470	
AAG ATG TAT GAA GGT GGA GAG CCC GAT GAT GTC GGG GGC CTA CTG GAT	13911
Lys Met Tyr Glu Gly Gly Glu Pro Asp Asp Val Gly Gly Leu Leu Asp	
4475 4480 4485 4490	
GCT GAT TTT GCC CTT GAC CCT GAC AAG CCT ACC AAC TTC ACC AAC CCA	13959
Ala Asp Phe Ala Leu Asp Pro Asp Lys Pro Thr Asn Phe Thr Asn Pro	
4495 4500 4505	
GTG TAT GCC ACG CTC TAC ATG GGG GGC CAC GGC AGC CGC CAT TCC CTG	14007
Val Tyr Ala Thr Leu Tyr Met Gly Gly His Gly Ser Arg His Ser Leu	
4510 4515 4520	

FIG. 6a

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GCC AGC ACG GAC GAG AAG CGA GAA CTG CTG GGC CGG GGA CCT GAA GAC 14055
Ala Ser Thr Asp Glu Lys Arg Glu Leu Leu Gly Arg Gly Pro Glu Asp
4525 4530 4535

GAG ATA GGA GAT CCC TTG GCA TAGGGCCCTG CCCCCACGGA TGTCCCCAGA AAGC 14110
CCCCCTGCCAC ATGAGTCTTT CAATGAACCC CCTCCCCAGC CGGCCCTTCT CGGGCCCTGC 14170
Glu Ile Gly Asp Pro Leu Ala
4540 4545

CGGGTGTACA AATGTAAAAA TGAAGGAATT ACTTTTATA TGTGAGCGAG CAAGCGAGCA 14230
AGCACAGTAT TATCTCTTTG CATTCCCTTC CTGCCTGCTC CTCAGTATCC CCCCCATGCT 14290
GCCTTGAGGG GGCAGGGAGG GCTTTGTGGC TCAAAGGTAT GAAGGAGTCC ACATGTTCCC 14350
TACCGAGCAT ACCCCTGGAA GCCTGGCGGC ACGGCCTCCC CACCACGCCGT GTGCAAGACA 14410
CTCAACGGGG CTCCGTGTCC CAGCTTCCT TTCCCTGGCT CTCTGGGTT AGTCAGGGG 14470
AGGTGGAGTC CTCTGCTGAC CCTGCTCTGGA AGATTTGGCT CTAGCTGAGG AAGGAGTCTT 14530
TTAGTTGAGG GAAGTCACCC CAAACCCAG CTCCCACCTT CAGGGCACC TCTCAGATGG 14590
CCATGCTCAG TATCCCTTCC AGACAGGCC TCCCCCTCTCT AGCGCCCCCT CTGTGGCTCC 14650
TAGGGCTGAA CACATTCTT GGTAACGTGTC CCCCAAGCCT CCCATCCCCC TGAGGGCCAG 14710
GAAGAGTCGG GGCACACCAA GGAAGGGCAA GCAGGGCAGCC CCATTGGG GACGTGAACG 14770
TTTTAATAAT TTTGCTGAA TTCTTACA ACTAAATAAC ACAGATATTG TTATAAAATAA 14830
AATTGTAAAA AAAAAAAA

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FIG. 6a

Met Leu Thr Pro Pro Leu Leu Leu Val Pro Leu Leu Ser Ala Leu
 1 5 10 15
 Val Ser Gly Ala Thr Met Asp Ala Pro Lys Thr Cys Ser Pro Lys Gln
 20 25 30
 Phe Ala Cys Arg Asp Gln Ile Thr Cys Ile Ser Lys Gly Trp Arg Cys
 35 40 45
 Asp Gly Glu Arg Asp Cys Pro Asp Gly Ser Asp Glu Ala Pro Glu Ile
 50 55 60
 Cys Pro Gln Ser Lys Ala Gln Arg Cys Pro Pro Asn Glu His Ser Cys
 65 70 75 80
 Leu Gly Thr Glu Leu Cys Val Pro Met Ser Arg Leu Cys Asn Gly Ile
 85 90 95
 Gln Asp Cys Met Asp Gly Ser Asp Glu Gly Ala His Cys Arg Glu Leu
 100 105 110
 Arg Ala Asn Cys Ser Arg Met Gly Cys Gln His His Cys Val Pro Thr
 115 120 125
 Pro Ser Gly Pro Thr Cys Tyr Cys Asn Ser Ser Phe Gln Leu Glu Ala
 130 135 140
 Asp Gly Lys Thr Cys Lys Asp Phe Asp Glu Cys Ser Val Tyr Gly Thr
 145 150 155 160
 Cys Ser Gln Leu Cys Thr Asn Thr Asp Gly Ser Phe Thr Cys Gly Cys
 165 170 175
 Val Glu Gly Tyr Leu Leu Gln Pro Asp Asn Arg Ser Cys Lys Ala Lys
 180 185 190
 Asn Glu Pro Val Asp Arg Pro Pro Val Leu Leu Ile Ala Asn Ser Gln
 195 200 205
 Asn Ile Leu Ala Thr Tyr Leu Ser Gly Ala Gln Val Ser Thr Ile Thr
 210 215 220
 Pro Thr Ser Thr Arg Gln Thr Thr Ala Met Asp Phe Ser Tyr Ala Asn
 225 230 235 240
 Glu Thr Val Cys Trp Val His Val Gly Asp Ser Ala Ala Gln Thr Gln
 245 250 255
 Leu Lys Cys Ala Arg Met Pro Gly Leu Lys Gly Phe Val Asp Glu His
 260 265 270
 Thr Ile Asn Ile Ser Leu Ser Leu His His Val Glu Gln Met Ala Ile
 275 280 285
 Asp Trp Leu Thr Gly Asn Phe Tyr Phe Val Asp Asp Ile Asp Asp Arg
 290 295 300
 Ile Phe Val Cys Asn Arg Asn Gly Asp Thr Cys Val Thr Leu Leu Asp
 305 310 315 320
 Leu Glu Leu Tyr Asn Pro Lys Gly Ile Ala Leu Asp Pro Ala Met Gly
 325 330 335
 Lys Val Phe Phe Thr Asp Tyr Gly Gln Ile Pro Lys Val Glu Arg Cys
 340 345 350
 Asp Met Asp Gly Gln Asn Arg Thr Lys Leu Val Asp Ser Lys Ile Val
 355 360 365
 Phe Pro His Gly Ile Thr Leu Asp Leu Val Ser Arg Leu Val Tyr Trp
 370 375 380
 Ala Asp Ala Tyr Leu Asp Tyr Ile Glu Val Val Asp Tyr Glu Gly Lys
 385 390 395 400
 Gly Arg Gln Thr Ile Ile Gln Gly Ile Leu Ile Glu His Leu Tyr Gly
 405 410 415
 Leu Thr Val Phe Glu Asn Tyr Leu Tyr Ala Thr Asn Ser Asp Asn Ala
 420 425 430
 Asn Thr Gln Gln Lys Thr Ser Val Ile Arg Val Asn Arg Phe Asn Ser
 435 440 445
 Thr Glu Tyr Gln Val Val Thr Arg Val Asp Lys Gly Gly Ala Leu His
 450 455 460

FIG. 6b

Ile Tyr His Gln Arg Arg Gln Pro Arg Val Arg Ser His Ala Cys Glu
 465 470 475 480
 Asn Asp Gln Tyr Gly Lys Pro Gly Gly Cys Ser Asp Ile Cys Leu Leu
 485 490 495
 Ala Asn Ser His Lys Ala Arg Thr Cys Arg Cys Arg Ser Gly Phe Ser
 500 505 510
 Leu Gly Ser Asp Gly Lys Ser Cys Lys Pro Glu His Glu Leu Phe
 515 520 525
 Leu Val Tyr Gly Lys Gly Arg Pro Gly Ile Ile Arg Gly Met Asp Met
 530 535 540
 Gly Ala Lys Val Pro Asp Glu His Met Ile Pro Ile Glu Asn Leu Met
 545 550 555 560
 Asn Pro Arg Ala Leu Asp Phe His Ala Glu Thr Gly Phe Ile Tyr Phe
 565 570 575
 Ala Asp Thr Thr Ser Tyr Leu Ile Gly Arg Gln Lys Ile Asp Gly Thr
 580 585 590
 Glu Arg Glu Thr Ile Leu Lys Asp Gly Ile His Asn Val Glu Gly Val
 595 600 605
 Ala Val Asp Trp Met Gly Asp Asn Leu Tyr Trp Thr Asp Asp Gly Pro
 610 615 620
 Lys Lys Thr Ile Ser Val Ala Arg Leu Glu Lys Ala Ala Gln Thr Arg
 625 630 635 640
 Lys Thr Leu Ile Glu Gly Lys Met Thr His Pro Arg Ala Ile Val Val
 645 650 655
 Asp Pro Leu Asn Gly Trp Met Tyr Trp Thr Asp Trp Glu Glu Asp Pro
 660 665 670
 Lys Asp Ser Arg Arg Gly Arg Leu Glu Arg Ala Trp Met Asp Gly Ser
 675 680 685
 His Arg Asp Ile Phe Val Thr Ser Lys Thr Val Leu Trp Pro Asn Gly
 690 695 700
 Leu Ser Leu Asp Ile Pro Ala Gly Arg Leu Tyr Trp Val Asp Ala Phe
 705 710 715 720
 Tyr Asp Arg Ile Glu Thr Ile Leu Leu Asn Gly Thr Asp Arg Lys Ile
 725 730 735
 Val Tyr Glu Gly Pro Glu Leu Asn His Ala Phe Gly Leu Cys His His
 740 745 750
 Gly Asn Tyr Leu Phe Trp Thr Glu Tyr Arg Ser Gly Ser Val Tyr Arg
 755 760 765
 Leu Glu Arg Gly Val Ala Gly Ala Pro Pro Thr Val Thr Leu Leu Arg
 770 775 780
 Ser Glu Arg Pro Pro Ile Phe Glu Ile Arg Met Tyr Asp Ala His Glu
 785 790 795 800
 Gln Gln Val Gly Thr Asn Lys Cys Arg Val Asn Asn Gly Gly Cys Ser
 805 810 815
 Ser Leu Cys Leu Ala Thr Pro Gly Ser Arg Gln Cys Ala Cys Ala Glu
 820 825 830
 Asp Gln Val Leu Asp Thr Asp Gly Val Thr Cys Leu Ala Asn Pro Ser
 835 840 845
 Tyr Val Pro Pro Gln Cys Gln Pro Gly Gln Phe Ala Cys Ala Asn
 850 855 860
 Asn Arg Cys Ile Gln Glu Arg Trp Lys Cys Asp Gly Asp Asn Asp Cys
 865 870 875 880
 Leu Asp Asn Ser Asp Glu Ala Pro Ala Leu Cys His Gln His Thr Cys
 885 890 895
 Pro Ser Asp Arg Phe Lys Cys Glu Asn Asn Arg Cys Ile Pro Asn Arg
 900 905 910
 Trp Leu Cys Asp Gly Asp Asn Asp Cys Gly Asn Ser Glu Asp Glu Ser
 915 920 925

FIG. 6b

Asn Ala Thr Cys Ser Ala Arg Thr Cys Pro Pro Asn Gln Phe Ser Cys
 930 935 940
 Ala Ser Gly Arg Cys Ile Pro Ile Ser Trp Thr Cys Asp Leu Asp Asp
 945 950 955 960
 Asp Cys Gly Asp Arg Ser Asp Glu Ser Ala Ser Cys Ala Tyr Pro Thr
 965 970 975
 Cys Phe Pro Leu Thr Gln Phe Thr Cys Asn Asn Gly Arg Cys Ile Asn
 980 985 990
 Ile Asn Trp Arg Cys Asp Asn Asp Cys Gly Asp Asn Ser Asp
 995 1000 1005
 Glu Ala Gly Cys Ser His Ser Cys Ser Ser Thr Gln Phe Lys Cys Asn
 1010 1015 1020
 Ser Gly Arg Cys Ile Pro Glu His Trp Thr Cys Asp Gly Asp Asn Asp
 1025 1030 1035 1040
 Cys Gly Asp Tyr Ser Asp Glu Thr His Ala Asn Cys Thr Asn Gln Ala
 1045 1050 1055
 Thr Arg Pro Pro Gly Gly Cys His Ser Asp Glu Phe Gln Cys Pro Leu
 1060 1065 1070
 Asp Gly Leu Cys Ile Pro Leu Arg Trp Arg Cys Asp Gly Asp Thr Asp
 1075 1080 1085
 Cys Met Asp Ser Ser Asp Glu Lys Ser Cys Glu Gly Val Thr His Val
 1090 1095 1100
 Cys Asp Pro Asn Val Lys Phe Gly Cys Lys Asp Ser Ala Arg Cys Ile
 1095 1110 1115 1120
 Ser Lys Ala Trp Val Cys Asp Gly Asp Ser Asp Cys Glu Asp Asn Ser
 1125 1130 1135
 Asp Glu Glu Asn Cys Glu Ala Leu Ala Cys Arg Pro Pro Ser His Pro
 1140 1145 1150
 Cys Ala Asn Asn Thr Ser Val Cys Leu Pro Pro Asp Lys Leu Cys Asp
 1155 1160 1165
 Gly Lys Asp Asp Cys Gly Asp Gly Ser Asp Glu Gly Glu Leu Cys Asp
 1170 1175 1180
 Gln Cys Ser Leu Asn Asn Gly Gly Cys Ser His Asn Cys Ser Val Ala
 1185 1190 1195 1200
 Pro Gly Glu Gly Ile Val Cys Ser Cys Pro Leu Gly Met Glu Leu Gly
 1205 1210 1215
 Ser Asp Asn His Thr Cys Gln Ile Gln Ser Tyr Cys Ala Lys His Leu
 1220 1225 1230
 Lys Cys Ser Gln Lys Cys Asp Gln Asn Lys Phe Ser Val Lys Cys Ser
 1235 1240 1245
 Cys Tyr Glu Gly Trp Val Leu Glu Pro Asp Gly Glu Thr Cys Arg Ser
 1250 1255 1260
 Leu Asp Pro Phe Lys Leu Phe Ile Ile Phe Ser Asn Arg His Glu Ile
 1265 1270 1275 1280
 Arg Arg Ile Asp Leu His Lys Gly Asp Tyr Ser Val Leu Val Pro Gly
 1285 1290 1295
 Leu Arg Asn Thr Ile Ala Leu Asp Phe His Leu Ser Gln Ser Ala Leu
 1300 1305 1310
 Tyr Trp Thr Asp Ala Val Glu Asp Lys Ile Tyr Arg Gly Lys Leu Leu
 1315 1320 1325
 Asp Asn Gly Ala Leu Thr Ser Phe Glu Val Val Ile Gln Tyr Gly Leu
 1330 1335 1340
 Ala Thr Pro Glu Gly Leu Ala Val Asp Trp Ile Ala Gly Asn Ile Tyr
 1345 1350 1355 1360
 Trp Val Glu Ser Asn Leu Asp Gln Ile Glu Val Ala Lys Leu Asp Gly
 1365 1370 1375
 Thr Leu Arg Thr Thr Leu Leu Ala Gly Asp Ile Glu His Pro Arg Ala
 1380 1385 1390
 Ile Ala Leu Asp Pro Arg Asp Gly Ile Leu Phe Trp Thr Asp Trp Asp

1395	1400	1405
Ala Ser Leu Pro Arg Ile Glu Ala Ala Ser Met Ser Gly Ala Gly Arg		
1410	1415	1420
Arg Thr Ile His Arg Glu Thr Gly Ser Gly Gly Cys Ala Asn Gly Leu		
425	1430	1435
Thr Val Asp Tyr Leu Glu Lys Arg Ile Leu Trp Ile Asp Ala Arg Ser		1440
1445	1450	1455
Asp Ala Ile Tyr Ser Ala Arg Tyr Asp Gly Ser Gly His Met Glu Val		
1460	1465	1470
Leu Arg Gly His Glu Phe Leu Ser His Pro Phe Ala Val Thr Leu Tyr		
1475	1480	1485
Gly Gly Glu Val Tyr Trp Thr Asp Trp Arg Thr Asn Thr Leu Ala Lys		
1490	1495	1500
Ala Asn Lys Trp Thr Gly His Asn Val Thr Val Val Gln Arg Thr Asn		
505	1510	1515
Thr Gln Pro Phe Asp Leu Gln Val Tyr His Pro Ser Arg Gln Pro Met		1520
1525	1530	1535
Ala Pro Asn Pro Cys Glu Ala Asn Gly Gly Arg Gly Pro Cys Ser His		
1540	1545	1550
Leu Cys Leu Ile Asn Tyr Asn Arg Thr Val Ser Trp Ala Cys Pro His		
1555	1560	1565
Leu Met Lys Leu His Lys Asp Asn Thr Thr Cys Tyr Glu Phe Lys Lys		
1570	1575	1580
Phe Leu Leu Tyr Ala Arg Gln Met Glu Ile Arg Gly Val Asp Leu Asp		
585	1590	1595
Ala Pro Tyr Tyr Asn Tyr Ile Ile Ser Phe Thr Val Pro Asp Ile Asp		1600
1605	1610	1615
Asn Val Thr Val Leu Asp Tyr Asp Ala Arg Glu Gln Arg Val Tyr Trp		
1620	1625	1630
Ser Asp Val Arg Thr Gln Ala Ile Lys Arg Ala Phe Ile Asn Gly Thr		
1635	1640	1645
Gly Val Glu Thr Val Val Ser Ala Asp Leu Pro Asn Ala His Gly Leu		
1650	1655	1660
Ala Val Asp Trp Val Ser Arg Asn Leu Phe Trp Thr Ser Tyr Asp Thr		
665	1670	1675
Asn Lys Lys Gln Ile Asn Val Ala Arg Leu Asp Gly Ser Phe Lys Asn		1680
1685	1690	1695
Ala Val Val Gln Gly Leu Glu Gln Pro His Gly Leu Val Val His Pro		
1700	1705	1710
Leu Arg Gly Lys Leu Tyr Trp Thr Asp Gly Asp Asn Ile Ser Met Ala		
1715	1720	1725
Asn Met Asp Gly Ser Asn His Thr Leu Leu Phe Ser Gly Gln Lys Gly		
1730	1735	1740
Pro Val Gly Leu Ala Ile Asp Phe Pro Glu Ser Lys Leu Tyr Trp Ile		
745	1750	1755
Ser Ser Gly Asn His Thr Ile Asn Arg Cys Asn Leu Asp Gly Ser Glu		1760
1765	1770	1775
Leu Glu Val Ile Asp Thr Met Arg Ser Gln Leu Gly Lys Ala Thr Ala		
1780	1785	1790
Leu Ala Ile Met Gly Asp Lys Leu Trp Trp Ala Asp Gln Val Ser Glu		
1795	1800	1805
Lys Met Gly Thr Cys Asn Lys Ala Asp Gly Ser Gly Ser Val Val Leu		
1810	1815	1820
Arg Asn Ser Thr Thr Leu Val Met His Met Lys Val Tyr Asp Glu Ser		
825	1830	1835
Ile Gln Leu Glu His Glu Gly Thr Asn Pro Cys Ser Val Asn Asn Gly		1840
1845	1850	1855
Asp Cys Ser Gln Leu Cys Leu Pro Thr Ser Glu Thr Thr Arg Ser Cys		
1860	1865	1870

FIG. 6b

Met Cys Thr Ala Gly Tyr Ser Leu Arg Ser Gly Gln Gln Ala Cys Glu
 1875 1880 1885
 Gly Val Gly Ser Phe Leu Leu Tyr Ser Val His Glu Gly Ile Arg Gly
 1890 1895 1900
 Ile Pro Leu Asp Pro Asn Asp Lys Ser Asp Ala Leu Val Pro Val Ser
 905 1910 1915 1920
 Gly Thr Ser Leu Ala Val Gly Ile Asp Phe His Ala Glu Asn Asp Thr
 1925 1930 1935
 Ile Tyr Trp Val Asp Met Gly Leu Ser Thr Ile Ser Arg Ala Lys Arg
 1940 1945 1950
 Asp Gln Thr Trp Arg Glu Asp Val Val Thr Asn Gly Ile Gly Arg Val
 1955 1960 1965
 Glu Gly Ile Ala Val Asp Trp Ile Ala Gly Asn Ile Tyr Trp Thr Asp
 1970 1975 1980
 Gln Gly Phe Asp Val Ile Glu Val Ala Arg Leu Asn Gly Ser Phe Arg
 985 1990 1995 2000
 Tyr Val Val Ile Ser Gln Gly Leu Asp Lys Pro Arg Ala Ile Thr Val
 2005 2010 2015
 His Pro Glu Lys Gly Tyr Leu Phe Trp Thr Glu Trp Gly His Tyr Pro
 2020 2025 2030
 Arg Ile Glu Arg Ser Arg Leu Asp Gly Thr Glu Arg Val Val Leu Val
 2035 2040 2045
 Asn Val Ser Ile Ser Trp Pro Asn Gly Ile Ser Val Asp Tyr Gln Gly
 2050 2055 2060
 Gly Lys Leu Tyr Trp Cys Asp Ala Arg Met Asp Lys Ile Glu Arg Ile
 065 2070 2075 2080
 Asp Leu Glu Thr Gly Glu Asn Arg Glu Val Val Leu Ser Ser Asn Asn
 2085 2090 2095
 Met Asp Met Phe Ser Val Ser Val Phe Glu Asp Phe Ile Tyr Trp Ser
 2100 2105 2110
 Asp Arg Thr His Ala Asn Gly Ser Ile Lys Arg Gly Cys Lys Asp Asn
 2115 2120 2125
 Ala Thr Asp Ser Val Pro Leu Arg Thr Gly Ile Gly Val Gln Leu Lys
 2130 2135 2140
 Asp Ile Lys Val Phe Asn Arg Asp Arg Gln Lys Gly Thr Asn Val Cys
 145 2150 2155 2160
 Ala Val Ala Asn Gly Gly Cys Gln Gln Leu Cys Leu Tyr Arg Gly Gly
 2165 2170 2175
 Gly Gln Arg Ala Cys Ala Cys Ala His Gly Met Leu Ala Glu Asp Gly
 2180 2185 2190
 Ala Ser Cys Arg Glu Tyr Ala Gly Tyr Leu Leu Tyr Ser Glu Arg Thr
 2195 2200 2205
 Ile Leu Lys Ser Ile His Leu Ser Asp Glu Arg Asn Leu Asn Ala Pro
 2210 2215 2220
 Val Gln Pro Phe Glu Asp Pro Glu His Met Lys Asn Val Ile Ala Leu
 2225 2230 2235 2240
 Ala Phe Asp Tyr Arg Ala Gly Thr Ser Pro Gly Thr Pro Asn Arg Ile
 2245 2250 2255
 Phe Phe Ser Asp Ile His Phe Gly Asn Ile Gln Gln Ile Asn Asp Asp
 2260 2265 2270
 Gly Ser Gly Arg Thr Thr Ile Val Glu Asn Val Gly Ser Val Glu Gly
 2275 2280 2285
 Leu Ala Tyr His Arg Gly Trp Asp Thr Leu Tyr Trp Thr Ser Tyr Thr
 2290 2295 2300
 Thr Ser Thr Ile Thr Arg His Thr Val Asp Gln Thr Arg Pro Gly Ala
 305 2310 2315 2320
 Phe Glu Arg Glu Thr Val Ile Thr Met Ser Gly Asp Asp His Pro Arg
 2325 2330 2335
 Ala Phe Val Leu Asp Glu Cys Gln Asn Leu Met Phe Trp Thr Asn Trp

2340	2345	2350
Asn Glu Leu His Pro Ser Ile Met Arg Ala Ala Leu Ser Gly Ala Asn		
2355	2360	2365
Val Leu Thr Leu Ile Glu Lys Asp Ile Arg Thr Pro Asn Gly Leu Ala		
2370	2375	2380
Ile Asp His Arg Ala Glu Lys Leu Tyr Phe Ser Asp Ala Thr Leu Asp		
385	2390	2395
Lys Ile Glu Arg Cys Glu Tyr Asp Gly Ser His Arg Tyr Val Ile Leu		
2405	2410	2415
Lys Ser Glu Pro Val His Pro Phe Gly Leu Ala Val Tyr Gly Glu His		
2420	2425	2430
Ile Phe Trp Thr Asp Trp Val Arg Arg Ala Val Gln Arg Ala Asn Lys		
2435	2440	2445
Tyr Val Gly Ser Asp Met Lys Leu Leu Arg Val Asp Ile Pro Gln Gln		
2450	2455	2460
Pro Met Gly Ile Ile Ala Val Ala Asn Asp Thr Asn Ser Cys Glu Leu		
465	2470	2475
Ser Pro Cys Arg Ile Asn Asn Gly Gly Cys Gln Asp Leu Cys Leu Leu		
2485	2490	2495
Thr His Gln Gly His Val Asn Cys Ser Cys Arg Gly Gly Arg Ile Leu		
2500	2505	2510
Gln Glu Asp Phe Thr Cys Arg Ala Val Asn Ser Ser Cys Arg Ala Gln		
2515	2520	2525
Asp Glu Phe Glu Cys Ala Asn Gly Glu Cys Ile Ser Phe Ser Leu Thr		
2530	2535	2540
Cys Asp Gly Val Ser His Cys Lys Asp Lys Ser Asp Glu Lys Pro Ser		
545	2550	2555
Tyr Cys Asn Ser Arg Arg Cys Lys Lys Thr Phe Arg Gln Cys Asn Asn		
2565	2570	2575
Gly Arg Cys Val Ser Asn Met Leu Trp Cys Asn Gly Val Asp Tyr Cys		
2580	2585	2590
Gly Asp Gly Ser Asp Glu Ile Pro Cys Asn Lys Thr Ala Cys Gly Val		
2595	2600	2605
Gly Glu Phe Arg Cys Arg Asp Gly Ser Cys Ile Gly Asn Ser Ser Arg		
2610	2615	2620
Cys Asn Gln Phe Val Asp Cys Glu Asp Ala Ser Asp Glu Met Asn Cys		
625	2630	2635
Ser Ala Thr Asp Cys Ser Ser Tyr Phe Arg Leu Gly Val Lys Gly Val		
2645	2650	2655
Leu Phe Gln Pro Cys Glu Arg Thr Ser Leu Cys Tyr Ala Pro Ser Trp		
2660	2665	2670
Val Cys Asp Gly Ala Asn Asp Cys Gly Asp Tyr Ser Asp Glu Arg Asp		
2675	2680	2685
Cys Pro Gly Val Lys Arg Pro Arg Cys Pro Leu Asn Tyr Phe Ala Cys		
2690	2695	2700
Pro Ser Gly Arg Cys Ile Pro Met Ser Trp Thr Cys Asp Lys Glu Asp		
705	2710	2715
Asp Cys Glu Asn Gly Glu Asp Glu Thr His Cys Asn Lys Phe Cys Ser		
2725	2730	2735
Glu Ala Gln Phe Glu Cys Gln Asn His Arg Cys Ile Ser Lys Gln Trp		
2740	2745	2750
Leu Cys Asp Gly Ser Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ala		
2755	2760	2765
His Cys Glu Gly Lys Thr Cys Gly Pro Ser Ser Phe Ser Cys Pro Gly		
2770	2775	2780
Thr His Val Cys Val Pro Glu Arg Trp Leu Cys Asp Gly Asp Lys Asp		
785	2790	2795
Cys Thr Asp Gly Ala Asp Glu Ser Val Thr Ala Gly Cys Leu Tyr Asn		
2805	2810	2815

FIG. 6b

Ser Thr Cys Asp Asp Arg Glu Phe Met Cys Gln Asn Arg Leu Cys Ile
 2820 2825 2830
 Pro Lys His Phe Val Cys Asp His Asp Arg Asp Cys Ala Asp Gly Ser
 2835 2840 2845
 Asp Glu Ser Pro Glu Cys Glu Tyr Pro Thr Cys Gly Pro Asn Glu Phe
 2850 2855 2860
 Arg Cys Ala Asn Gly Arg Cys Leu Ser Ser Arg Gln Trp Glu Cys Asp
 865 2870 2875 2880
 Gly Glu Asn Asp Cys His Asp His Ser Asp Glu Ala Pro Lys Asn Pro
 2885 2890 2895
 His Cys Thr Ser Pro Glu His Lys Cys Asn Ala Ser Ser Gln Phe Leu
 2900 2905 2910
 Cys Ser Ser Gly Arg Cys Val Ala Glu Ala Leu Leu Cys Asn Gly Gln
 2915 2920 2925
 Asp Asp Cys Gly Asp Gly Ser Asp Glu Arg Gly Cys His Val Asn Glu
 2930 2935 2940
 Cys Leu Ser Arg Lys Leu Ser Gly Cys Ser Gln Asp Cys Glu Asp Leu
 945 2950 2955 2960
 Lys Ile Gly Phe Lys Cys Arg Cys Arg Pro Gly Phe Arg Leu Lys Asp
 2965 2970 2975
 Asp Gly Arg Thr Cys Ala Asp Leu Asp Glu Cys Ser Thr Thr Phe Pro
 2980 2985 2990
 Cys Ser Gln Leu Cys Ile Asn Thr His Gly Ser Tyr Lys Cys Leu Cys
 2995 3000 3005
 Val Glu Gly Tyr Ala Pro Arg Gly Gly Asp Pro His Ser Cys Lys Ala
 3010 3015 3020
 Val Thr Asp Glu Glu Pro Phe Leu Ile Phe Ala Asn Arg Tyr Tyr Leu
 025 3030 3035 3040
 Arg Lys Leu Asn Leu Asp Gly Ser Asn Tyr Thr Leu Leu Lys Gln Gly
 3045 3050 3055
 Leu Asn Asn Ala Val Ala Leu Ala Phe Asp Tyr Arg Glu Gln Met Ile
 3060 3065 3070
 Tyr Trp Thr Gly Val Thr Thr Gln Gly Ser Met Ile Arg Arg Met His
 3075 3080 3085
 Leu Asn Gly Ser Asn Val Gln Val Leu His Arg Thr Gly Leu Ser Asn
 3090 3095 3100
 Pro Asp Gly Leu Ala Val Asp Trp Val Gly Gly Asn Leu Tyr Trp Cys
 105 3110 3115 3120
 Asp Lys Gly Arg Asp Thr Ile Glu Val Ser Lys Leu Asn Gly Ala Tyr
 3125 3130 3135
 Arg Thr Val Leu Val Ser Ser Gly Leu Arg Glu Pro Arg Ala Leu Val
 3140 3145 3150
 Val Asp Val Gln Asn Gly Tyr Leu Tyr Trp Thr Asp Trp Gly Asp His
 3155 3160 3165
 Ser Leu Ile Gly Arg Ile Gly Met Asp Gly Ser Gly Arg Ser Ile Ile
 3170 3175 3180
 Val Asp Thr Lys Ile Thr Trp Pro Asn Gly Leu Thr Val Asp Tyr Val
 185 3190 3195 3200
 Thr Glu Arg Ile Tyr Trp Ala Asp Ala Arg Glu Asp Tyr Ile Glu Phe
 3205 3210 3215
 Ala Ser Leu Asp Gly Ser Asn Arg His Val Val Leu Ser Gln Asp Ile
 3220 3225 3230
 Pro His Ile Phe Ala Leu Thr Leu Phe Glu Asp Tyr Val Tyr Trp Thr
 3235 3240 3245
 Asp Trp Glu Thr Lys Ser Ile Asn Arg Ala His Lys Thr Thr Gly Ala
 3250 3255 3260
 Asn Lys Thr Leu Leu Ile Ser Thr Leu His Arg Pro Met Asp Leu His
 265 3270 3275 3280
 Val Phe His Ala Leu Arg Gin Pro Asp Val Pro Asn His Pro Cys Lys

3285	3290	3295
Val Asn Asn Gly Gly Cys Ser Asn Leu Cys Leu Leu Ser Pro Gly Gly		
3300	3305	3310
Gly His Lys Cys Ala Cys Pro Thr Asn Phe Tyr Leu Gly Gly Asp Gly		
3315	3320	3325
Arg Thr Cys Val Ser Asn Cys Thr Ala Ser Gln Phe Val Cys Lys Asn		
3330	3335	3340
Asp Lys Cys Ile Pro Phe Trp Trp Lys Cys Asp Thr Glu Asp Asp Cys		
3345	3350	3355
Gly Asp His Ser Asp Glu Pro Pro Asp Cys Pro Glu Phe Lys Cys Arg		
3365	3370	3375
Pro Gly Gln Phe Gln Cys Ser Thr Gly Ile Cys Thr Asn Pro Ala Phe		
3380	3385	3390
Ile Cys Asp Gly Asp Asn Asp Cys Gln Asp Asn Ser Asp Glu Ala Asn		
3395	3400	3405
Cys Asp Ile His Val Cys Leu Pro Ser Gln Phe Lys Cys Thr Asn Thr		
3410	3415	3420
Asn Arg Cys Ile Pro Gly Ile Phe Arg Cys Asn Gly Gln Asp Asn Cys		
3425	3430	3435
Gly Asp Gly Glu Asp Glu Arg Asp Cys Pro Glu Val Thr Cys Ala Pro		
3445	3450	3455
Asn Gln Phe Gln Cys Ser Ile Thr Lys Arg Cys Ile Pro Arg Val Trp		
3460	3465	3470
Val Cys Asp Arg Asp Asn His Cys Val Asp Gly Ser Asp Glu Pro Ala		
3475	3480	3485
Asn Cys Thr Gln Met Thr Cys Gly Val Asp Glu Phe Arg Cys Lys Asp		
3490	3495	3500
Ser Gly Arg Cys Ile Pro Ala Arg Trp Lys Cys Asp Gly Glu Asp Asp		
3505	3510	3515
Cys Gly Asp Gly Ser Asp Glu Pro Lys Glu Glu Cys Asp Glu Arg Thr		
3525	3530	3535
Cys Glu Pro Tyr Gln Phe Arg Cys Lys Asn Asn Arg Cys Val Pro Gly		
3540	3545	3550
Arg Trp Gln Cys Asp Tyr Asp Asn Asp Cys Gly Asp Asn Ser Asp Glu		
3555	3560	3565
Glu Ser Cys Thr Pro Arg Pro Cys Ser Glu Ser Glu Phe Phe Cys Ala		
3570	3575	3580
Asn Gly Arg Cys Ile Ala Gly Arg Trp Lys Cys Asp Gly Asp His Asp		
3585	3590	3595
Cys Ala Asp Gly Ser Asp Glu Lys Asp Cys Thr Pro Arg Cys Asp Met		
3605	3610	3615
Asp Gln Phe Gln Cys Lys Ser Gly His Cys Ile Pro Leu Arg Trp Pro		
3620	3625	3630
Cys Asp Ala Asp Ala Asp Cys Met Asp Gly Ser Asp Glu Glu Ala Cys		
3635	3640	3645
Gly Thr Gly Val Arg Thr Cys Pro Leu Asp Glu Phe Gln Cys Asn Asn		
3650	3655	3660
Thr Leu Cys Lys Pro Leu Ala Trp Lys Cys Asp Gly Glu Asp Asp Cys		
3665	3670	3675
Gly Asp Asn Ser Asp Glu Asn Pro Glu Glu Cys Ala Arg Phe Ile Cys		
3685	3690	3695
Pro Pro Asn Arg Pro Phe Arg Cys Lys Asn Asp Arg Val Cys Leu Trp		
3700	3705	3710
Ile Gly Arg Gln Cys Asp Gly Val Asp Asn Cys Gly Asp Gly Thr Asp		
3715	3720	3725
Glu Glu Asp Cys Glu Pro Pro Thr Ala Gln Asn Pro His Cys Lys Asp		
3730	3735	3740
Lys Lys Glu Phe Leu Cys Arg Asn Gln Arg Cys Leu Ser Ser Ser Leu		
745	3750	3755
		3760

FIG. 6b

Arg Cys Asn Met Phe Asp Asp Cys Gly Asp Gly Ser Asp Glu Glu Asp
 3765 3770 3775
 Cys Ser Ile Asp Pro Lys Leu Thr Ser Cys Ala Thr Asn Ala Ser Met
 3780 3785 3790
 Cys Gly Asp Glu Ala Arg Cys Val Arg Thr Glu Lys Ala Ala Tyr Cys
 3795 3800 3805
 Ala Cys Arg Ser Gly Phe His Thr Val Pro Gly Gln Pro Gly Cys Gln
 3810 3815 3820
 Asp Ile Asn Glu Cys Leu Arg Phe Gly Thr Cys Ser Gln Leu Trp Asn
 825 3830 3835 3840
 Lys Pro Lys Gly Gly His Leu Cys Ser Cys Ala Arg Asn Phe Met Lys
 3845 3850 3855
 Thr His Asn Thr Cys Lys Ala Glu Gly Ser Glu Tyr Gln Val Leu Tyr
 3860 3865 3870
 Ile Ala Asp Asp Asn Glu Ile Arg Ser Leu Phe Pro Gly His Pro His
 3875 3880 3885
 Ser Ala Tyr Glu Gln Thr Phe Gln Gly Asp Glu Ser Val Arg Ile Asp
 3890 3895 3900
 Ala Met Asp Val His Val Lys Ala Gly Arg Val Tyr Trp Thr Asn Trp
 905 3910 3915 3920
 His Thr Gly Thr Ile Ser Tyr Arg Ser Leu Pro Pro Ala Ala Pro Pro
 3925 3930 3935
 Thr Thr Ser Asn Arg His Arg Arg Gln Ile Asp Arg Gly Val Thr His
 3940 3945 3950
 Leu Asn Ile Ser Gly Leu Lys Met Pro Arg Gly Ile Ala Ile Asp Trp
 3955 3960 3965
 Val Ala Gly Asn Val Tyr Trp Thr Asp Ser Gly Arg Asp Val Ile Glu
 3970 3975 3980
 Val Ala Gln Met Lys Gly Glu Asn Arg Lys Thr Leu Ile Ser Gly Met
 985 3990 3995 4000
 Ile Asp Glu Pro His Ala Ile Val Val Asp Pro Leu Arg Gly Thr Met
 4005 4010 4015
 Tyr Trp Ser Asp Trp Gly Asn His Pro Lys Ile Glu Thr Ala Ala Met
 4020 4025 4030
 Asp Gly Thr Leu Arg Glu Thr Leu Val Gln Asp Asn Ile Gln Trp Pro
 4035 4040 4045
 Thr Gly Leu Ala Val Asp Tyr His Asn Glu Arg Leu Tyr Trp Ala Asp
 4050 4055 4060
 Ala Lys Leu Ser Val Ile Gly Ser Ile Arg Leu Asn Gly Thr Asp Pro
 065 4070 4075 4080
 Ile Val Ala Ala Asp Ser Lys Arg Gly Leu Ser His Pro Phe Ser Ile
 4085 4090 4095
 Asp Val Phe Glu Asp Tyr Ile Tyr Gly Val Thr Tyr Ile Asn Asn Arg
 4100 4105 4110
 Val Phe Lys Ile His Lys Phe Gly His Ser Pro Leu Tyr Asn Leu Thr
 4115 4120 4125
 Gly Gly Leu Ser His Ala Ser Asp Val Val Leu Tyr His Gln His Lys
 4130 4135 4140
 Gln Pro Glu Val Thr Asn Pro Cys Asp Arg Lys Lys Cys Glu Trp Leu
 145 4150 4155 4160
 Cys Leu Leu Ser Pro Ser Gly Pro Val Cys Thr Cys Pro Asn Gly Lys
 4165 4170 4175
 Arg Leu Asp Asn Gly Thr Cys Val Pro Val Pro Ser Pro Thr Pro Pro
 4180 4185 4190
 Pro Asp Ala Pro Arg Pro Gly Thr Cys Thr Leu Gln Cys Phe Asn Gly
 4195 4200 4205
 Gly Ser Cys Phe Leu Asn Ala Arg Arg Gln Pro Lys Cys Arg Cys Gln
 4210 4215 4220
 Pro Arg Tyr Thr Gly Asp Lys Glu Leu Asp Gln Cys Trp Glu Tyr

FIG. 6b

225	4230	4235	4240
Cys His Asn Gly Gly Thr Cys Ala Ala Ser Pro Ser Gly Met Pro Thr			
4245	4250	4255	
Cys Arg Cys Pro Thr Gly Phe Thr Gly Pro Lys Cys Thr Ala Gln Val			
4260	4265	4270	
Cys Ala Gly Tyr Cys Ser Asn Asn Ser Thr Cys Thr Val Asn Gln Gly			
4275	4280	4285	
Asn Gln Pro Gln Cys Arg Cys Leu Pro Gly Phe Leu Gly Asp Arg Cys			
4290	4295	4300	
Gln Tyr Arg Gln Cys Ser Gly Phe Cys Glu Asn Phe Gly Thr Cys Gln			
305	4310	4315	4320
Met Ala Ala Asp Gly Ser Arg Gln Cys Arg Cys Thr Val Tyr Phe Glu			
4325	4330	4335	
Gly Pro Arg Cys Glu Val Asn Lys Cys Ser Arg Cys Leu Gln Gly Ala			
4340	4345	4350	
Cys Val Val Asn Lys Gln Thr Gly Asp Val Thr Cys Asn Cys Thr Asp			
4355	4360	4365	
Gly Arg Val Ala Pro Ser Cys Leu Thr Cys Ile Asp His Cys Ser Asn			
4370	4375	4380	
Gly Gly Ser Cys Thr Met Asn Ser Lys Met Met Pro Glu Cys Gln Cys			
385	4390	4395	4400
Pro Pro His Met Thr Gly Pro Arg Cys Gln Glu Gln Val Val Ser Gln			
4405	4410	4415	
Gln Gln Pro Gly His Met Ala Ser Ile Leu Ile Pro Leu Leu Leu			
4420	4425	4430	
Leu Leu Leu Leu Val Ala Gly Val Val Phe Trp Tyr Lys Arg Arg			
4435	4440	4445	
Val Arg Gly Ala Lys Gly Phe Gln His Gln Arg Met Thr Asn Gly Ala			
4450	4455	4460	
Met Asn Val Glu Ile Gly Asn Pro Thr Tyr Lys Met Tyr Glu Gly Gly			
465	4470	4475	4480
Glu Pro Asp Asp Val Gly Gly Leu Leu Asp Ala Asp Phe Ala Leu Asp			
4485	4490	4495	
Pro Asp Lys Pro Thr Asn Phe Thr Asn Pro Val Tyr Ala Thr Leu Tyr			
4500	4505	4510	
Met Gly Gly His Gly Ser Arg His Ser Leu Ala Ser Thr Asp Glu Lys			
4515	4520	4525	
Arg Glu Leu Leu Gly Arg Gly Pro Glu Asp Glu Ile Gly Asp Pro Leu			
4530	4535	4540	
Ala			
545			

GCTACAATCC ATCTGGTCTC CTCCAGCTCC TTCTTCTGC AAC ATG GGG AAG AAC Met Gly Lys Asn 1	55
AAA CTC CTT CAT CCA AGT CTG GTT CTT CTC CTC TTG GTC CTC CTG CCC Lys Leu Leu His Pro Ser Leu Val Leu Leu Leu Val Leu Leu Pro 5 10 15 20	103
ACA GAC GCC TCA GTC TCT GGA AAA CCG CAG TAT ATG GTT CTG GTC CCC Thr Asp Ala Ser Val Ser Gly Lys Pro Gln Tyr Met Val Leu Val Pro 25 30 35	151
TCC CTG CTC CAC ACT GAG ACC ACT GAG AAG GGC TGT GTC CTT CTG AGC Ser Leu Leu His Thr Glu Thr Thr Glu Lys Gly Cys Val Leu Leu Ser 40 45 50	199
TAC CTG AAT GAG ACA GTG ACT GTA AGT GCT TCC TTG GAG TCT GTC AGG Tyr Leu Asn Glu Thr Val Thr Val Ser Ala Ser Leu Glu Ser Val Arg 55 60 65	247
GGA AAC AGG AGC CTC TTC ACT GAC CTG GAG GCG GAG AAT GAC GTA CTC Gly Asn Arg Ser Leu Phe Thr Asp Leu Glu Ala Glu Asn Asp Val Leu 70 75 80	295
CAC TGT GTC GCC TTC GCT GTC CCA AAG TCT TCA TCC AAT GAG GAG GTA His Cys Val Ala Phe Ala Val Pro Lys Ser Ser Asn Glu Glu Val 85 90 95 100	343
ATG TTC CTC ACT GTC CAA GTG AAA GGA CCA ACC CAA GAA TTT AAG AAG Met Phe Leu Thr Val Gln Val Lys Gly Pro Thr Gln Glu Phe Lys Lys 105 110 115	391
CGG ACC ACA GTG ATG GTT AAG AAC GAG GAC AGT CTG GTC TTT GTC CAG Arg Thr Thr Val Met Val Lys Asn Glu Asp Ser Leu Val Phe Val Gln 120 125 130	439
ACA GAC AAA TCA ATC TAC AAA CCA GGG CAG ACA GTG AAA TTT CGT GTT Thr Asp Lys Ser Ile Tyr Lys Pro Gly Gln Thr Val Lys Phe Arg Val 135 140 145	487
GTC TCC ATG GAT GAA AAC TTT CAC CCC CTG AAT GAG TTG ATT CCA CTA Val Ser Met Asp Glu Asn Phe His Pro Leu Asn Glu Leu Ile Pro Leu 150 155 160	535
GTA TAC ATT CAG GAT CCC AAA GGA AAT CGC ATC GCA CAA TGG CAG AGT Val Tyr Ile Gln Asp Pro Lys Gly Asn Arg Ile Ala Gln Trp Gln Ser 165 170 175 180	583
TTC CAG TTA GAG GGT GGC CTC AAG CAA TTT TCT TTT CCC CTC TCA TCA Phe Gln Leu Glu Gly Gly Leu Lys Gln Phe Ser Phe Pro Leu Ser Ser 185 190 195	631
GAG CCC TTC CAG GGC TCC TAC AAG GTG GTG GTA CAG AAG AAA TCA GGT Glu Pro Phe Gln Gly Ser Tyr Lys Val Val Gln Lys Lys Ser Gly 200 205 210	679
GGA AGG ACA GAG CAC CCT TTC ACC GTG GAG GAA TTT GTT CTT CCC AAG	727

FIG. 7a

Gly Arg Thr Glu His Pro Phe Thr Val Glu Glu Phe Val Leu Pro Lys		
215	220	225
TTT GAA GTA CAA GTA ACA GTG CCA AAG ATA ATC ACC ATC TTG GAA GAA		775
Phe Glu Val Gln Val Thr Val Pro Lys Ile Ile Thr Ile Leu Glu Glu		
230	235	240
GAG ATG AAT GTA TCA GTG TGT GGC CTA TAC ACA TAT GGG AAG CCT GTC		823
Glu Met Asn Val Ser Val Cys Gly Leu Tyr Thr Tyr Gly Lys Pro Val		
245	250	255
CCT GGA CAT GTG ACT GTG AGC ATT TGC AGA AAG TAT AGT GAC GCT TCC		871
Pro Gly His Val Thr Val Ser Ile Cys Arg Lys Tyr Ser Asp Ala Ser		
265	270	275
GAC TGC CAC GGT GAA GAT TCA CAG GCT TTC TGT GAG AAA TTC AGT GGA		919
Asp Cys His Gly Glu Asp Ser Gln Ala Phe Cys Glu Lys Phe Ser Gly		
280	285	290
CAG CTA AAC AGC CAT GGC TGC TTC TAT CAG CAA GTA AAA ACC AAG GTC		967
Gln Leu Asn Ser His Gly Cys Phe Tyr Gln Gln Val Lys Thr Lys Val		
295	300	305
TTC CAG CTG AAG AGG AAG GAG TAT GAA ATG AAA CTT CAC ACT GAG GCC		1015
Phe Gln Leu Lys Arg Lys Glu Tyr Glu Met Lys Leu His Thr Glu Ala		
310	315	320
CAG ATC CAA GAA GAA GGA ACA GTG GTG GAA TTG ACT GGA AGG CAG TCC		1063
Gln Ile Gln Glu Glu Gly Thr Val Val Glu Leu Thr Gly Arg Gln Ser		
325	330	335
340		
AGT GAA ATC ACA AGA ACC ATA ACC AAA CTC TCA TTT GTG AAA GTG GAC		1111
Ser Glu Ile Thr Arg Thr Ile Thr Lys Leu Ser Phe Val Lys Val Asp		
345	350	355
TCA CAC TTT CGA CAG GGA ATT CCC TTC TTT GGG CAG GTG CGC CTA GTA		1159
Ser His Phe Arg Gln Gly Ile Pro Phe Phe Gly Gln Val Arg Leu Val		
360	365	370
GAT GGG AAA GGC GTC CCT ATA CCA AAT AAA GTC ATA TTC ATC AGA GGA		1207
Asp Gly Lys Gly Val Pro Ile Pro Asn Lys Val Ile Phe Ile Arg Gly		
375	380	385
AAT GAA GCA AAC TAT TAC TCC AAT GCT ACC ACG GAT GAG CAT GGC CTT		1255
Asn Glu Ala Asn Tyr Tyr Ser Asn Ala Thr Thr Asp Glu His Gly Leu		
390	395	400
GTA CAG TTC TCT ATC AAC ACC ACC AAC GTT ATG GGT ACC TCT CTT ACT		1303
Val Gln Phe Ser Ile Asn Thr Thr Asn Val Met Gly Thr Ser Leu Thr		
405	410	415
420		
GTT AGG GTC AAT TAC AAG GAT CGT AGT CCC TGT TAC GGC TAC CAG TGG		1351
Val Arg Val Asn Tyr Lys Asp Arg Ser Pro Cys Tyr Gly Tyr Gln Trp		
425	430	435
GTG TCA GAA GAA CAC GAA GAG GCA CAT CAC ACT GCT TAT CTT GTG TTC		1399
Val Ser Glu Glu His Glu Ala His His Thr Ala Tyr Leu Val Phe		
440	445	450

FIG. 7a

TCC CCA AGC AAG AGC TTT GTC CAC CTT GAG CCC ATG TCT CAT GAA CTA	1447
Ser Pro Ser Lys Ser Phe Val His Leu Glu Pro Met Ser His Glu Leu	
455 460 465	
CCC TGT GGC CAT ACT CAG ACA GTC CAG GCA CAT TAT ATT CTG AAT GGA	1495
Pro Cys Gly His Thr Gln Thr Val Gln Ala His Tyr Ile Leu Asn Gly	
470 475 480	
GGC ACC CTG CTG GGG CTG AAG AAG CTC TCC TTT TAT TAT CTG ATA ATG	1543
Gly Thr Leu Leu Gly Leu Lys Leu Ser Phe Tyr Tyr Leu Ile Met	
485 490 495 500	
GCA AAG GGA GGC ATT GTC CGA ACT GGG ACT CAT GGA CTG CTT GTG AAG	1591
Ala Lys Gly Ile Val Arg Thr Gly Thr His Gly Leu Leu Val Lys	
505 510 515	
CAG GAA GAC ATG AAG GGC CAT TTT TCC ATC TCA ATC CCT GTG AAG TCA	1639
Gln Glu Asp Met Lys Gly His Phe Ser Ile Ser Ile Pro Val Lys Ser	
520 525 530	
GAC ATT GCT CCT GTC GCT CGG TTG CTC ATC TAT GCT GTT TTA CCT ACC	1687
Asp Ile Ala Pro Val Ala Arg Leu Leu Ile Tyr Ala Val Leu Pro Thr	
535 540 545	
GGG GAC GTG ATT GGG GAT TCT GCA AAA TAT GAT GTT GAA AAT TGT CTG	1735
Gly Asp Val Ile Gly Asp Ser Ala Lys Tyr Asp Val Glu Asn Cys Leu	
550 555 560	
GCC AAC AAG GTG GAT TTG AGC TTC AGC CCA TCA CAA AGT CTC CCA GCC	1783
Ala Asn Lys Val Asp Leu Ser Phe Ser Pro Ser Gln Ser Leu Pro Ala	
565 570 575 580	
TCA CAC GCC CAC CTG CGA GTC ACA GCG GCT CCT CAG TCC GTC TGC GCC	1831
Ser His Ala His Leu Arg Val Thr Ala Ala Pro Gln Ser Val Cys Ala	
585 590 595	
CTC CGT GCT GTG GAC CAA AGC GTG CTG CTC ATG AAG CCT GAT GCT GAG	1879
Leu Arg Ala Val Asp Gln Ser Val Leu Leu Met Lys Pro Asp Ala Glu	
600 605 610	
CTC TCG GCG TCC TCG GTT TAC AAC CTG CTA CCA GAA AAG GAC CTC ACT	1927
Leu Ser Ala Ser Ser Val Tyr Asn Leu Leu Pro Glu Lys Asp Leu Thr	
615 620 625	
GGC TTC CCT GGG CCT TTG AAT GAC CAG GAC GAT GAA GAC TGC ATC AAT	1975
Gly Phe Pro Gly Pro Leu Asn Asp Gln Asp Asp Glu Asp Cys Ile Asn	
630 635 640	
CGT CAT AAT GTC TAT ATT AAT GGA ATC ACA TAT ACT CCA GTA TCA AGT	2023
Arg His Asn Val Tyr Ile Asn Gly Ile Thr Tyr Thr Pro Val Ser Ser	
645 650 655 660	
ACA AAT GAA AAG GAT ATG TAC AGC TTC CTA GAG GAC ATG GGC TTA AAG	2071
Thr Asn Glu Lys Asp Met Tyr Ser Phe Leu Glu Asp Met Gly Leu Lys	
665 670 675	
GCA TTC ACC AAC TCA AAG ATT CGT AAA CCC AAA ATG TGT CCA CAG CTT	2119
Ala Phe Thr Asn Ser Lys Ile Arg Lys Pro Lys Met Cys Pro Gln Leu	
680 685 690	

FIG. 7a

CAA CAG TAT GAA ATG CAT GGA CCT GAA GGT CTA CGT GTA GGT TTT TAT Gln Gln Tyr Glu Met His Gly Pro Glu Gly Leu Arg Val Gly Phe Tyr 695 700 705	2167
GAG TCA GAT GTA ATG GGA AGA GGC CAT GCA CGC CTG GTG CAT GTT GAA Glu Ser Asp Val Met Gly Arg Gly His Ala Arg Leu Val His Val Glu 710 715 720	2215
GAG CCT CAC ACG GAG ACC GTA CGA AAG TAC TTC CCT GAG ACA TGG ATC Glu Pro His Thr Glu Thr Val Arg Lys Tyr Phe Pro Glu Thr Trp Ile 725 730 735 740	2263
TGG GAT TTG GTG GTG GTA AAC TCA GCA GGG GTG GCT GAG GTA GGA GTA Trp Asp Leu Val Val Asn Ser Ala Gly Val Ala Glu Val Gly Val 745 750 755	2311
ACA GTC CCT GAC ACC ATC ACC GAG TGG AAG GCA GGG GCC TTC TGC CTG Thr Val Pro Asp Thr Ile Thr Glu Trp Lys Ala Gly Ala Phe Cys Leu 760 765 770	2359
TCT GAA GAT GCT GGA CTT GGT ATC TCT TCC ACT GCC TCT CTC CGA GCC Ser Glu Asp Ala Gly Leu Gly Ile Ser Ser Thr Ala Ser Leu Arg Ala 775 780 785	2407
TTC CAG CCC TTC TTT GTG GAG CTT ACA ATG CCT TAC TCT GTG ATT CGT Phe Gln Pro Phe Val Glu Leu Thr Met Pro Tyr Ser Val Ile Arg 790 795 800	2455
GGA GAG GCC TTC ACA CTC AAG GCC ACG GTC CTA AAC TAC CTT CCC AAA Gly Glu Ala Phe Thr Leu Lys Ala Thr Val Leu Asn Tyr Leu Pro Lys 805 810 815 820	2503
TGC ATC CGG GTC AGT GTG CAG CTG GAA GCC TCT CCC GCC TTC CTT GCT Cys Ile Arg Val Ser Val Gln Leu Glu Ala Ser Pro Ala Phe Leu Ala 825 830 835	2551
GTC CCA GTG GAG AAG GAA CAA GCG CCT CAC TGC ATC TGT GCA AAC GGG Val Pro Val Glu Lys Glu Gln Ala Pro His Cys Ile Cys Ala Asn Gly 840 845 850	2599
CGG CAA ACT GTG TCC TGG GCA GTA ACC CCA AAG TCA TTA GGA AAT GTG Arg Gln Thr Val Ser Trp Ala Val Thr Pro Lys Ser Leu Gly Asn Val 855 860 865	2647
AAT TTC ACT GTG AGC GCA GAG GCA CTA GAG TCT CAA GAG CTG TGT GGG Asn Phe Thr Val Ser Ala Glu Ala Leu Glu Ser Gln Glu Leu Cys Gly 870 875 880	2695
ACT GAG GTG CCT TCA GTT CCT GAA CAC GGA AGG AAA GAC ACA GTC ATC Thr Glu Val Pro Ser Val Pro Glu His Gly Arg Lys Asp Thr Val Ile 885 890 895 900	2743
AAG CCT CTG TTG GTT GAA CCT GAA GGA CTA GAG AAG GAA ACA ACA TTC Lys Pro Leu Leu Val Glu Pro Glu Gly Leu Glu Lys Glu Thr Thr Phe 905 910 915	2791
AAC TCC CTA CTT TGT CCA TCA GGT GGT GAG GTT TCT GAA GAA TTA TCC Asn Ser Leu Leu Cys Pro Ser Gly Gly Glu Val Ser Glu Glu Leu Ser 920 925 930	2839

FIG. 7a

CTG AAA CTG CCA CCA AAT GTG GTA GAA GAA TCT GCC CGA GCT TCT GTC Leu Lys Leu Pro Pro Asn Val Val Glu Glu Ser Ala Arg Ala Ser Val 935 940 945	2887
TCA GTT TTG GGA GAC ATA TTA GGC TCT GCC ATG CAA AAC ACA CAA AAT Ser Val Leu Gly Asp Ile Leu Gly Ser Ala Met Gln Asn Thr Gln Asn 950 955 960	2935
CTT CTC CAG ATG CCC TAT GGC TGT GGA GAG CAG AAT ATG GTC CTC TTT Leu Leu Gln Met Pro Tyr Gly Cys Gly Glu Gln Asn Met Val Leu Phe 965 970 975 980	2983
GCT CCT AAC ATC TAT GTA CTG GAT TAT CTA AAT GAA ACA CAG CAG CTT Ala Pro Asn Ile Tyr Val Leu Asp Tyr Leu Asn Glu Thr Gln Gln Leu 985 990 995	3031
ACT CCA GAG GTC AAG TCC AAG GCC ATT GGC TAT CTC AAC ACT GGT TAC Thr Pro Glu Val Lys Ser Lys Ala Ile Gly Tyr Leu Asn Thr Gly Tyr 1000 1005 1010	3079
CAG AGA CAG TTG AAC TAC AAA CAC TAT GAT GGC TCC TAC AGC ACC TTT Gln Arg Gln Leu Asn Tyr Lys His Tyr Asp Gly Ser Tyr Ser Thr Phe 1015 1020 1025	3127
GGG GAG CGA TAT GGC AGG AAC CAG GGC AAC ACC TGG CTC ACA GCC TTT Gly Glu Arg Tyr Gly Arg Asn Gln Gly Asn Thr Trp Leu Thr Ala Phe 1030 1035 1040	3175
GTT CTG AAG ACT TTT GCC CAA GCT CGA GCC TAC ATC TTC ATC GAT GAA Val Leu Lys Thr Phe Ala Gln Ala Arg Ala Tyr Ile Phe Ile Asp Glu 1045 1050 1055 1060	3223
GCA CAC ATT ACC CAA GCC CTC ATA TGG CTC TCC CAG AGG CAG AAG GAC Ala His Ile Thr Gln Ala Leu Ile Trp Leu Ser Gln Arg Gln Lys Asp 1065 1070 1075	3271
AAT GGC TGT TTC AGG AGC TCT GGG TCA CTG CTC AAC AAT GCC ATA AAG Asn Gly Cys Phe Arg Ser Ser Gly Ser Leu Leu Asn Asn Ala Ile Lys 1080 1085 1090	3319
GGA GGA GTA GAA GAT GAA GTG ACC CTC TCC GCC TAT ATC ACC ATC GCC Gly Gly Val Glu Asp Glu Val Thr Leu Ser Ala Tyr Ile Thr Ile Ala 1095 1100 1105	3367
CTT CTG GAG ATT CCT CTC ACA GTC ACT CAC CCT GTT GTC CGC AAT GCC Leu Leu Glu Ile Pro Leu Thr Val Thr His Pro Val Val Arg Asn Ala 1110 1115 1120	3415
CTG TTT TGC CTG GAG TCA GCC TGG AAG ACA GCA CAA GAA GGG GAC CAT Leu Phe Cys Leu Glu Ser Ala Trp Lys Thr Ala Gln Glu Gly Asp His 1125 1130 1135 1140	3463
GGC AGC CAT GTA TAT ACC AAA GCA CTG CTG GCC TAT GCT TTT GCC CTG Gly Ser His Val Tyr Thr Lys Ala Leu Leu Ala Tyr Ala Phe Ala Leu 1145 1150 1155	3511
GCA GGT AAC CAG GAC AAG AGG AAG GAA GTA CTC AAG TCA CTT AAT GAG Ala Gly Asn Gln Asp Lys Arg Lys Glu Val Leu Lys Ser Leu Asn Glu 1160 1165 1170	3559

FIG. 7a

GAA GCT GTG AAG AAA GAC AAC TCT GTC CAT TGG GAG CGC CCT CAG AAA Glu Ala Val Lys Lys Asp Asn Ser Val His Trp Glu Arg Pro Gln Lys 1175 1180 1185	3607
CCC AAG GCA CCA GTG GGG CAT TTT TAC GAA CCC CAG GCT CCC TCT GCT Pro Lys Ala Pro Val Gly His Phe Tyr Glu Pro Gln Ala Pro Ser Ala 1190 1195 1200	3655
GAG GTG GAG ATG ACA TCC TAT GTG CTC CTC GCT TAT CTC ACG GCC CAG Glu Val Glu Met Thr Ser Tyr Val Leu Leu Ala Tyr Leu Thr Ala Gln 1205 1210 1215 1220	3703
CCA GCC CCA ACC TCG GAG GAC CTG ACC TCT GCA ACC AAC ATC GTG AAG Pro Ala Pro Thr Ser Glu Asp Leu Thr Ser Ala Thr Asn Ile Val Lys 1225 1230 1235	3751
TGG ATC ACG AAG CAG CAG AAT GCC CAG GGC GGT TTC TCC TCC ACC CAG Trp Ile Thr Lys Gln Gln Asn Ala Gln Gly Gly Phe Ser Ser Thr Gln 1240 1245 1250	3799
GAC ACA GTG GTG GCT CTC CAT GCT CTG TCC AAA TAT GGA GCC GCC ACA Asp Thr Val Val Ala Leu His Ala Leu Ser Lys Tyr Gly Ala Ala Thr 1255 1260 1265	3847
TTT ACC AGG ACT GGG AAG GCT GCA CAG GTG ACT ATC CAG TCT TCA GGG Phe Thr Arg Thr Gly Lys Ala Ala Gln Val Thr Ile Gln Ser Ser Gly 1270 1275 1280	3895
ACA TTT TCC AGC AAA TTC CAA GTG GAC AAC AAC AAT CGC CTG TTA CTG Thr Phe Ser Ser Lys Phe Gln Val Asp Asn Asn Asn Arg Leu Leu Leu 1285 1290 1295 1300	3943
CAG CAG GTC TCA TTG CCA GAG CTG CCT GGG GAA TAC AGC ATG AAA GTG Gln Gln Val Ser Leu Pro Glu Leu Pro Gly Glu Tyr Ser Met Lys Val 1305 1310 1315	3991
ACA GGA GAA GGA TGT GTC TAC CTC CAG ACC TCC TTG AAA TAC AAT ATT Thr Gly Glu Gly Cys Val Tyr Leu Gln Thr Ser Leu Lys Tyr Asn Ile 1320 1325 1330	4039
CTC CCA GAA AAG GAA GAG TTC CCC TTT GCT TTA GGA GTG CAG ACT CTG Leu Pro Glu Lys Glu Glu Phe Pro Phe Ala Leu Gly Val Gln Thr Leu 1335 1340 1345	4087
CCT CAA ACT TGT GAT GAA CCC AAA GCC CAC ACC AGC TTC CAA ATC TCC Pro Gln Thr Cys Asp Glu Pro Lys Ala His Thr Ser Phe Gln Ile Ser 1350 1355 1360	4135
CTA AGT GTC AGT TAC ACA GGG AGC CGC TCT GCC TCC AAC ATG GCG ATC Leu Ser Val Ser Tyr Thr Gly Ser Arg Ser Ala Ser Asn Met Ala Ile 1365 1370 1375 1380	4183
GTT GAT GTG AAG ATG GTC TCT GGC TTC ATT CCC CTG AAG CCA ACA GTG Val Asp Val Lys Met Val Ser Gly Phe Ile Pro Leu Lys Pro Thr Val 1385 1390 1395	4231
AAA ATG CTT GAA AGA TCT AAC CAT GTG AGC CGG ACA GAA GTC AGC AGC Lys Met Leu Glu Arg Ser Asn His Val Ser Arg Thr Glu Val Ser Ser 1400 1405 1410	4279

FIG. 7a

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AAC CAT GTC TTG ATT TAC CTT GAT AAG GTG TCA AAT CAG ACA CTG AGC	4327
Asn His Val Leu Ile Tyr Leu Asp Lys Val Ser Asn Gln Thr Leu Ser	
1415 1420 1425	
TTG TTC TTC ACG GTT CTG CAA GAT GTC CCA GTA AGA GAT CTC AAA CCA	4375
Leu Phe Phe Thr Val Leu Gln Asp Val Pro Val Arg Asp Leu Lys Pro	
1430 1435 1440	
GCC ATA GTG AAA GTC TAT GAT TAC TAC GAG ACG GAT GAG TTT GCA ATC	4423
Ala Ile Val Lys Val Tyr Asp Tyr Tyr Glu Thr Asp Glu Phe Ala Ile	
1445 1450 1455 1460	
GCT GAG TAC AAT GCT CCT TGC AGC AAA GAT CTT GGA AAT GCT TGAAGACCA	4474
Ala Glu Tyr Asn Ala Pro Cys Ser Lys Asp Leu Gly Asn Ala	
1465 1470 1	
CAAGGCTGAA AAGTGCTTG CTGGAGTCCT GTTCTCTGAG CTCCACAGAA GACACGTGTT	4534
TTTGTATCTT TAAAGACTTG ATGAATAAAC ACTTTTCTG GTC	4577

FIG. 7a

Ser Val Ser Gly Lys Pro Gln Tyr Met Val Leu Val Pro Ser Leu Leu
 1 5 10 15
 His Thr Glu Thr Thr Glu Lys Gly Cys Val Leu Leu Ser Tyr Leu Asn
 20 25 30
 Glu Thr Val Thr Val Ser Ala Ser Leu Glu Ser Val Arg Gly Asn Arg
 35 40 45
 Ser Leu Phe Thr Asp Leu Glu Ala Glu Asn Asp Val Leu His Cys Val
 50 55 60
 Ala Phe Ala Val Pro Lys Ser Ser Asn Glu Glu Val Met Phe Leu
 65 70 75 80
 Thr Val Gln Val Lys Gly Pro Thr Gln Glu Phe Lys Lys Arg Thr Thr
 85 90 95
 Val Met Val Lys Asn Glu Asp Ser Leu Val Phe Val Gln Thr Asp Lys
 100 105 110
 Ser Ile Tyr Lys Pro Gly Gln Thr Val Lys Phe Arg Val Val Ser Met
 115 120 125
 Asp Glu Asn Phe His Pro Leu Asn Glu Leu Ile Pro Leu Val Tyr Ile
 130 135 140
 Gln Asp Pro Lys Gly Asn Arg Ile Ala Gln Trp Gln Ser Phe Gln Leu
 145 150 155 160
 Glu Gly Gly Leu Lys Gln Phe Ser Phe Pro Leu Ser Ser Glu Pro Phe
 165 170 175
 Gln Gly Ser Tyr Lys Val Val Val Gln Lys Lys Ser Gly Gly Arg Thr
 180 185 190
 Glu His Pro Phe Thr Val Glu Glu Phe Val Leu Pro Lys Phe Glu Val
 195 200 205
 Gln Val Thr Val Pro Lys Ile Ile Thr Ile Leu Glu Glu Glu Met Asn
 210 215 220
 Val Ser Val Cys Gly Leu Tyr Thr Tyr Gly Lys Pro Val Pro Gly His
 225 230 235 240
 Val Thr Val Ser Ile Cys Arg Lys Tyr Ser Asp Ala Ser Asp Cys His
 245 250 255
 Gly Glu Asp Ser Gln Ala Phe Cys Glu Lys Phe Ser Gly Gln Leu Asn
 260 265 270
 Ser His Gly Cys Phe Tyr Gln Gln Val Lys Thr Lys Val Phe Gln Leu
 275 280 285
 Lys Arg Lys Glu Tyr Glu Met Lys Leu His Thr Glu Ala Gln Ile Gln
 290 295 300
 Glu Glu Gly Thr Val Val Glu Leu Thr Gly Arg Gln Ser Ser Glu Ile
 305 310 315 320
 Thr Arg Thr Ile Thr Lys Leu Ser Phe Val Lys Val Asp Ser His Phe
 325 330 335
 Arg Gln Gly Ile Pro Phe Phe Gly Gln Val Arg Leu Val Asp Gly Lys
 340 345 350
 Gly Val Pro Ile Pro Asn Lys Val Ile Phe Ile Arg Gly Asn Glu Ala
 355 360 365
 Asn Tyr Tyr Ser Asn Ala Thr Thr Asp Glu His Gly Leu Val Gln Phe
 370 375 380
 Ser Ile Asn Thr Thr Asn Val Met Gly Thr Ser Leu Thr Val Arg Val
 385 390 395 400
 Asn Tyr Lys Asp Arg Ser Pro Cys Tyr Gly Tyr Gln Trp Val Ser Glu
 405 410 415
 Glu His Glu Glu Ala His His Thr Ala Tyr Leu Val Phe Ser Pro Ser
 420 425 430
 Lys Ser Phe Val His Leu Glu Pro Met Ser His Glu Leu Pro Cys Gly
 435 440 445
 His Thr Gln Thr Val Gln Ala His Tyr Ile Leu Asn Gly Gly Thr Leu
 450 455 460
 Leu Gly Leu Lys Lys Leu Ser Phe Tyr Tyr Leu Ile Met Ala Lys Gly

FIG. 7b

465	470	475	480
Gly Ile Val Arg Thr	Gly Thr His	Gly Leu Leu Val Lys	Gln Glu Asp
485	490	495	
Met Lys Gly His Phe Ser Ile Ser	Ile Pro Val Lys Ser Asp	Ile Ala	
500	505	510	
Pro Val Ala Arg Leu Leu Ile Tyr	Ala Val Leu Pro Thr	Gly Asp Val	
515	520	525	
Ile Gly Asp Ser Ala Lys Tyr Asp Val	Glu Asn Cys	Leu Ala Asn Lys	
530	535	540	
Val Asp Leu Ser Phe Ser Pro Ser	Gln Ser Leu Pro Ala Ser His	Ala	
545	550	555	560
His Leu Arg Val Thr Ala Ala Pro Gln	Ser Val Cys Ala Leu Arg	Ala	
565	570	575	
Val Asp Gln Ser Val Leu Leu Met	Lys Pro Asp Ala Glu	Leu Ser Ala	
580	585	590	
Ser Ser Val Tyr Asn Leu Leu Pro	Glu Lys Asp Leu Thr	Gly Phe Pro	
595	600	605	
Gly Pro Leu Asn Asp Gln Asp Asp	Glu Asp Cys Ile Asn Arg	His Asn	
610	615	620	
Val Tyr Ile Asn Gly Ile Thr Tyr	Thr Pro Val Ser Ser Thr Asn	Glu	
625	630	635	640
Lys Asp Met Tyr Ser Phe Leu Glu Asp	Met Gly Leu Lys Ala Phe	Thr	
645	650	655	
Asn Ser Lys Ile Arg Lys Pro Lys	Met Cys Pro Gln Leu Gln	Gln Tyr	
660	665	670	
Glu Met His Gly Pro Glu Gly Leu Arg	Val Gly Phe Tyr	Glu Ser Asp	
675	680	685	
Val Met Gly Arg Gly His Ala Arg	Leu Val His Val Glu	Glu Pro His	
690	695	700	
Thr Glu Thr Val Arg Lys Tyr	Phe Pro Glu Thr Trp	Ile Trp Asp	Leu
705	710	715	720
Val Val Val Asn Ser Ala Gly Val	Ala Glu Val Gly Val	Thr Val Pro	
725	730	735	
Asp Thr Ile Thr Glu Trp Lys Ala	Gly Ala Phe Cys	Leu Ser Glu Asp	
740	745	750	
Ala Gly Leu Gly Ile Ser Ser	Thr Ala Ser Leu Arg	Ala Phe Gln Pro	
755	760	765	
Phe Phe Val Glu Leu Thr Met	Pro Tyr Ser Val Ile Arg	Gly Glu Ala	
770	775	780	
Phe Thr Leu Lys Ala Thr Val Leu Asn	Tyr Leu Pro Lys Cys	Ile Arg	
785	790	795	800
Val Ser Val Gln Leu Glu Ala Ser	Pro Ala Phe Leu Ala Val	Pro Val	
805	810	815	
Glu Lys Glu Gln Ala Pro His	Cys Ile Cys Ala Asn	Gly Arg Gln Thr	
820	825	830	
Val Ser Trp Ala Val Thr Pro	Lys Ser Leu Gly Asn	Val Asn Phe	Thr
835	840	845	
Val Ser Ala Glu Ala Leu Glu	Ser Gln Glu Leu Cys	Gly Thr Glu Val	
850	855	860	
Pro Ser Val Pro Glu His	Gly Arg Lys Asp	Thr Val Ile Lys	Pro Leu
865	870	875	880
Leu Val Glu Pro Glu Gly Leu Glu	Lys Glu Thr Thr Phe	Asn Ser Leu	
885	890	895	
Leu Cys Pro Ser Gly Gly Glu Val	Ser Glu Glu Leu Ser	Leu Lys Leu	
900	905	910	
Pro Pro Asn Val Val Glu Glu Ser	Ala Arg Ala Ser Val	Ser Val Leu	
915	920	925	
Gly Asp Ile Leu Gly Ser Ala Met	Gln Asn Thr Gln	Asn Leu Leu Gln	
930	935	940	

Met Pro Tyr Gly Cys Gly Glu Gln Asn Met Val Leu Phe Ala Pro Asn
 945 950 955 960
 Ile Tyr Val Leu Asp Tyr Leu Asn Glu Thr Gln Gln Leu Thr Pro Glu
 965 970 975
 Val Lys Ser Lys Ala Ile Gly Tyr Leu Asn Thr Gly Tyr Gln Arg Gln
 980 985 990
 Leu Asn Tyr Lys His Tyr Asp Gly Ser Tyr Ser Thr Phe Gly Glu Arg
 995 1000 1005
 Tyr Gly Arg Asn Gln Gly Asn Thr Trp Leu Thr Ala Phe Val Leu Lys
 1010 1015 1020
 Thr Phe Ala Gln Ala Arg Ala Tyr Ile Phe Ile Asp Glu Ala His Ile
 025 1030 1035 1040
 Thr Gln Ala Leu Ile Trp Leu Ser Gln Arg Gln Lys Asp Asn Gly Cys
 1045 1050 1055
 Phe Arg Ser Ser Gly Ser Leu Leu Asn Asn Ala Ile Lys Gly Gly Val
 1060 1065 1070
 Glu Asp Glu Val Thr Leu Ser Ala Tyr Ile Thr Ile Ala Leu Leu Glu
 1075 1080 1085
 Ile Pro Leu Thr Val Thr His Pro Val Val Arg Asn Ala Leu Phe Cys
 1090 1095 1100
 Leu Glu Ser Ala Trp Lys Thr Ala Gln Glu Gly Asp His Gly Ser His
 105 1110 1115 1120
 Val Tyr Thr Lys Ala Leu Leu Ala Tyr Ala Phe Ala Leu Ala Gly Asn
 1125 1130 1135
 Gln Asp Lys Arg Lys Glu Val Leu Lys Ser Leu Asn Glu Glu Ala Val
 1140 1145 1150
 Lys Lys Asp Asn Ser Val His Trp Glu Arg Pro Gln Lys Pro Lys Ala
 1155 1160 1165
 Pro Val Gly His Phe Tyr Glu Pro Gln Ala Pro Ser Ala Glu Val Glu
 1170 1175 1180
 Met Thr Ser Tyr Val Leu Leu Ala Tyr Leu Thr Ala Gln Pro Ala Pro
 185 1190 1195 1200
 Thr Ser Glu Asp Leu Thr Ser Ala Thr Asn Ile Val Lys Trp Ile Thr
 1205 1210 1215
 Lys Gln Gln Asn Ala Gln Gly Gly Phe Ser Ser Thr Gln Asp Thr Val
 1220 1225 1230
 Val Ala Leu His Ala Leu Ser Lys Tyr Gly Ala Ala Thr Phe Thr Arg
 1235 1240 1245
 Thr Gly Lys Ala Ala Gln Val Thr Ile Gln Ser Ser Gly Thr Phe Ser
 1250 1255 1260
 Ser Lys Phe Gln Val Asp Asn Asn Arg Leu Leu Leu Gln Gln Val
 265 1270 1275 1280
 Ser Leu Pro Glu Leu Pro Gly Glu Tyr Ser Met Lys Val Thr Gly Glu
 1285 1290 1295
 Gly Cys Val Tyr Leu Gln Thr Ser Leu Lys Tyr Asn Ile Leu Pro Glu
 1300 1305 1310
Lys Glu Glu Phe Pro Phe Ala Leu Gly Val Gln Thr Ile Pro Gln Thr
 1315 1320 1325
Cys Asp Glu Pro Lys Ala His Thr Ser Phe Gln Ile Ser Leu Ser Val
 1330 1335 1340
Ser Tyr Thr Gly Ser Arg Ser Ala Ser Asn Met Ala Ile Val Asp Val
 345 1350 1355 1360
Lys Met Val Ser Gly Phe Ile Pro Leu Lys Pro Thr Val Lys Met Leu
 1365 1370 1375
Glu Arg Ser Asn His Val Ser Arg Thr Glu Val Ser Ser Asn His Val
 1380 1385 1390
Leu Ile Tyr Leu Asp Lys Val Ser Asn Gln Thr Leu Ser Leu Phe Phe
 1395 1400 1405

Thr Val Leu Gln Asp Val Pro Val Arg Asp Leu Lys Pro Ala Ile Val
1410 1415 1420
Lys Val Tyr Asp Tyr Tyr Glu Thr Asp Glu Phe Ala Ile Ala Glu Tyr
425 1430 1435 1440
Asn Ala Pro Cys Ser Lys Asp Leu Gly Asn Ala
1445 1450

FIG. 7b

CAGCGGTGCG	AGCTCCAGGC	CCATGCACTG	AGGAGGCGGA	AACAAGGGGA	GCCCCCAGAG	60
CTCCATCAAG	CCCCCTCCAA	AGGCTCCCCT	ACCCGGTCCA	CGCCCCCCCAC	CCCCCCTCCC	120
CGCCTCCTCC	CAATTGTGCA	TTTTGCGCAG	CGGAGGCGGC	TCCGAGATGG	GGCTGTGAGC	180
TTCGCCCGGG	GAGGGGGAAA	GAGCAGCGAG	GAGTGAAGCG	GGGGGGTGGG	GTGAAGGGTT	240
TGGATTTCGG	GGCAGGGGGC	GCACCCCGT	CAGCAGGCC	TCCCAAGGG	GCTCGGAACT	300
CTACCTCTTC	ACCCACGCC	CTGGTGCCT	TTGCCGAAGG	AAAGAATAAG	AACAGAGAAG	360
GAGGAGGGGG	AAAGGAGGAA	AAGGGGGACC	CCCCAAGCTGG	GGGGGGTGA	GGAGAGAAGT	420
AGCAGGACCA	GAGGGGAAGG	GGCTGCTGCT	TGCATCAGCC	CACACC	ATG CTG ACC	475
				Met	Leu Thr	
				1		
CCG CCG TTG CTC CTG CTG CTG CCC CTG CTC TCA GCT CTG GTC GCG GCG						523
Pro Pro Leu Leu Leu Leu Pro Leu Leu Ser Ala Leu Val Ala Ala						
5	10	15				
GCT ATC GAC GCC CCT AAG ACT TGC AGC CCC AAG CAG TTT GCC TGC AGA						571
Ala Ile Asp Ala Pro Lys Thr Cys Ser Pro Lys Gln Phe Ala Cys Arg						
20	25	30				35
GAT CAA ATA ACC TGT ATC TCA AAG GGC TGG CGG TGC GAC GGT GAG AGG						619
Asp Gln Ile Thr Cys Ile Ser Lys Gly Trp Arg Cys Asp Gly Glu Arg						
40	45	50				
GAC TGC CCA GAC GGA TCT GAC GAG GCC CCT GAG ATT TGT CCA CAG AGT						667
Asp Cys Pro Asp Gly Ser Asp Glu Ala Pro Glu Ile Cys Pro Gln Ser						
55	60	65				
AAG GCC CAG CGA TGC CAG CCA AAC GAG CAT AAC TGC CTG GGT ACT GAG						715
Lys Ala Gln Arg Cys Gln Pro Asn Glu His Asn Cys Leu Gly Thr Glu						
70	75	80				
CTG TGT GTT CCC ATG TCC CGC CTC TGC AAT GGG GTC CAG GAC TGC ATG						763
Leu Cys Val Pro Met Ser Arg Leu Cys Asn Gly Val Gln Asp Cys Met						
85	90	95				
GAC GGC TCA GAT GAG GGG CCC CAC TGC CGA GAG CTC CAA GGC AAC TGC						811
Asp Gly Ser Asp Glu Gly Pro His Cys Arg Glu Leu Gln Gly Asn Cys						
100	105	110				115
TCT CGC CTG GGC TGC CAG CAC CAT TGT GTC CCC ACA CTC GAT GGG CCC						859
Ser Arg Leu Gly Cys Gln His His Cys Val Pro Thr Leu Asp Gly Pro						
120	125	130				
ACC TGC TAC TGC AAC AGC AGC TTT CAG CTT CAG GCA GAT GGC AAG ACC						907
Thr Cys Tyr Cys Asn Ser Ser Phe Gln Leu Gln Ala Asp Gly Lys Thr						
135	140	145				
TGC AAA GAT TTT GAT GAG TGC TCA GTG TAC GGC ACC TGC AGC CAG CTA						955
Cys Lys Asp Phe Asp Glu Cys Ser Val Tyr Gly Thr Cys Ser Gln Leu						
150	155	160				
TGC ACC AAC ACA GAC GGC TCC TTC ATA TGT GGC TGT GTT GAA GGA TAC						1003
Cys Thr Asn Thr Asp Gly Ser Phe Ile Cys Gly Cys Val Glu Gly Tyr						
165	170	175				
CTC CTG CAG CCG GAT AAC CGC TCC TGC AAG GCC AAG AAC GAG CCA GTA						1051
Leu Leu Gln Pro Asp Asn Arg Ser Cys Lys Ala Lys Asn Glu Pro Val						
180	185	190				195

FIG. 8a

GAC CGG CCC CCT GTG CTG TTG ATA GCC AAC TCC CAG AAC ATC TTG GCC	1099
Asp Arg Pro Pro Val Leu Leu Ile Ala Asn Ser Gln Asn Ile Leu Ala	
200 205 210	
ACG TAC CTG AGT GGG GCC CAG GTG TCT ACC ATC ACA CCT ACG AGC ACG	1147
Thr Tyr Leu Ser Gly Ala Gln Val Ser Thr Ile Thr Pro Thr Ser Thr	
215 220 225	
CGG CAG ACC ACA GCC ATG GAC TTC AGC TAT GCC AAC GAG ACC GTA TGC	1195
Arg Gln Thr Thr Ala Met Asp Phe Ser Tyr Ala Asn Glu Thr Val Cys	
230 235 240	
TGG GTG CAT GTT GGG GAC AGT GCT GCT CAG ACG CAG CTC AAG TGT GCC	1243
Trp Val His Val Gly Asp Ser Ala Ala Gln Thr Gln Leu Lys Cys Ala	
245 250 255	
CGC ATG CCT GGC CTA AAG GGC TTC GTG GAT GAG CAC ACC ATC AAC ATC	1291
Arg Met Pro Gly Leu Lys Gly Phe Val Asp Glu His Thr Ile Asn Ile	
260 265 270 275	
TCC CTC AGT CTG CAC CAC GTG GAA CAG ATG GCC ATC GAC TGG CTG ACA	1339
Ser Leu Ser Leu His His Val Glu Gln Met Ala Ile Asp Trp Leu Thr	
280 285 290	
GGC AAC TTC TAC TTT GTG GAT GAC ATC GAT GAT AGG ATC TTT GTC TGC	1387
Gly Asn Phe Tyr Phe Val Asp Asp Ile Asp Asp Arg Ile Phe Val Cys	
295 300 305	
AAC AGA AAT GGG GAC ACA TGT GTC ACA TTG CTA GAC CTG GAA CTC TAC	1435
Asn Arg Asn Gly Asp Thr Cys Val Thr Leu Leu Asp Leu Glu Leu Tyr	
310 315 320	
AAC CCC AAG GGC ATT GCC CTG GAC CCT GCC ATG GGG AAG GTG TTT TTC	1483
Asn Pro Lys Gly Ile Ala Leu Asp Pro Ala Met Gly Lys Val Phe Phe	
325 330 335	
ACT GAC TAT GGG CAG ATC CCA AAG GTG GAA CGC TGT GAC ATG GAT GGG	1531
Thr Asp Tyr Gly Gln Ile Pro Lys Val Glu Arg Cys Asp Met Asp Gly	
340 345 350 355	
CAG AAC CGC ACC AAG CTC GTC GAC AGC AAG ATT GTG TTT CCT CAT GGC	1579
Gln Asn Arg Thr Lys Leu Val Asp Ser Lys Ile Val Phe Pro His Gly	
360 365 370	
ATC ACG CTG GAC CTG GTC AGC CGC CTT GTC TAC TGG GCA GAT GCC TAT	1627
Ile Thr Leu Asp Leu Val Ser Arg Leu Val Tyr Trp Ala Asp Ala Tyr	
375 380 385	
CTG GAC TAT ATT GAA GTG GTG GAC TAT GAG GGC AAG GGC CGC CAG ACC	1675
Leu Asp Tyr Ile Glu Val Val Asp Tyr Glu Gly Lys Gly Arg Gln Thr	
390 395 400	
ATC ATC CAG GGC ATC CTG ATT GAG CAC CTG TAC GGC CTG ACT GTG TTT	1723
Ile Ile Gln Gly Ile Leu Ile Glu His Leu Tyr Gly Leu Thr Val Phe	
405 410 415	
GAG AAT TAT CTC TAT GCC ACC AAC TCG GAC AAT GCC AAT GCC CAG CAG	1771
Glu Asn Tyr Leu Tyr Ala Thr Asn Ser Asp Asn Ala Asn Ala Gln Gln	
420 425 430 435	

FIG. 8a

AAG ACG AGT GTG ATC CGT GTG AAC CGC TTT AAC AGC ACC GAG TAC CAG Lys Thr Ser Val Ile Arg Val Asn Arg Phe Asn Ser Thr Glu Tyr Gln 440 445 450	1819
GTT GTC ACC CGG GTG GAC AAG GGT GGT GCC CTC CAC ATC TAC CAC CAG Val Val Thr Arg Val Asp Lys Gly Gly Ala Leu His Ile Tyr His Gln 455 460 465	1867
AGG CGT CAG CCC CGA GTG AGG AGC CAT GCC TGT GAA AAC GAC CAG TAT Arg Arg Gln Pro Arg Val Arg Ser His Ala Cys Glu Asn Asp Gln Tyr 470 475 480	1915
GGG AAG CCG GGT GGC TGC TCT GAC ATC TGC CTG CTG GCC AAC AGC CAC Gly Lys Pro Gly Gly Cys Ser Asp Ile Cys Leu Leu Ala Asn Ser His 485 490 495	1963
AAG GCG CGG ACC TGC CGC TGC CGT TCC GGC TTC AGC CTG GGC AGT GAC Lys Ala Arg Thr Cys Arg Cys Arg Ser Gly Phe Ser Leu Gly Ser Asp 500 505 510 515	2011
GGG AAG TCA TGC AAG AAG CCG GAG CAT GAG CTG TTC CTC GTG TAT GGC Gly Lys Ser Cys Lys Lys Pro Glu His Glu Leu Phe Leu Val Tyr Gly 520 525 530	2059
AAG GGC CGG CCA GGC ATC ATC CGG GGC ATG GAT ATG GGG GCC AAG GTC Lys Gly Arg Pro Gly Ile Ile Arg Gly Met Asp Met Gly Ala Lys Val 535 540 545	2107
CCG GAT GAG CAC ATG ATC CCC ATT GAA AAC CTC ATG AAC CCC CGA GCC Pro Asp Glu His Met Ile Pro Ile Glu Asn Leu Met Asn Pro Arg Ala 550 555 560	2155
CTG GAC TTC CAC GCT GAG ACC GGC TTC ATC TAC TTT GCC GAC ACC ACC Leu Asp Phe His Ala Glu Thr Gly Phe Ile Tyr Phe Ala Asp Thr Thr 565 570 575	2203
AGC TAC CTC ATT GGC CGC CAG AAG ATT GAT GGC ACT GAG CGG GAG ACC Ser Tyr Leu Ile Gly Arg Gln Lys Ile Asp Gly Thr Glu Arg Glu Thr 580 585 590 595	2251
ATC CTG AAG GAC GGC ATC CAC AAT GTG GAG GGT GTG GCC GTG GAC TGG Ile Leu Lys Asp Gly Ile His Asn Val Glu Gly Val Ala Val Asp Trp 600 605 610	2299
ATG GGA GAC AAT CTG TAC TGG ACG GAC GAT GGG CCC AAA AAG ACA ATC Met Gly Asp Asn Leu Tyr Trp Thr Asp Asp Gly Pro Lys Lys Thr Ile 615 620 625	2347
AGC GTG GCC AGG CTG GAG AAA GCT GCT CAG ACC CGC AAG ACT TTA ATC Ser Val Ala Arg Leu Glu Lys Ala Ala Gln Thr Arg Lys Thr Leu Ile 630 635 640	2395
GAG GGC AAA ATG ACA CAC CCC AGG GCT ATT GTG GTG GAT CCA CTC AAT Glu Gly Lys Met Thr His Pro Arg Ala Ile Val Val Asp Pro Leu Asn 645 650 655	2443
GGG TGG ATG TAC TGG ACA GAC TGG GAG GAG GAC CCC AAG GAC AGT CGG Gly Trp Met Tyr Trp Thr Asp Trp Glu Glu Asp Pro Lys Asp Ser Arg 660 665 670 675	2491

CGT GGG CGG CTG GAG AGG GCG TGG ATG GAT GGC TCA CAC CGA GAC ATC Arg Gly Arg Leu Glu Arg Ala Trp Met Asp Gly Ser His Arg Asp Ile 680 685 690	2539
TTT GTC ACC TCC AAG ACA GTG CTT TGG CCC AAT GGG CTA AGC CTG GAC Phe Val Thr Ser Lys Thr Val Leu Trp Pro Asn Gly Leu Ser Leu Asp 695 700 705	2587
ATC CCG GCT GGG CGC CTC TAC TGG GTG GAT GCC TTC TAC GAC CGC ATC Ile Pro Ala Gly Arg Leu Tyr Trp Val Asp Ala Phe Tyr Asp Arg Ile 710 715 720	2635
GAG ACG ATA CTG CTC AAT GGC ACA GAC CGG AAG ATT GTG TAT GAA GGT Glu Thr Ile Leu Leu Asn Gly Thr Asp Arg Lys Ile Val Tyr Glu Gly 725 730 735	2683
CCT GAG CTG AAC CAC GCC TTT GGC CTG TGT CAC CAT GGC AAC TAC CTC Pro Glu Leu Asn His Ala Phe Gly Leu Cys His His Gly Asn Tyr Leu 740 745 750 755	2731
TTC TGG ACT GAG TAT CGG AGT GGC AGT GTC TAC CGC TTG GAA CGG GGT Phe Trp Thr Glu Tyr Arg Ser Gly Ser Val Tyr Arg Leu Glu Arg Gly 760 765 770	2779
GTA GGA GGC GCA CCC CCC ACT GTG ACC CTT CTG CGC AGT GAG CGG CCC Val Gly Ala Pro Pro Thr Val Thr Leu Leu Arg Ser Glu Arg Pro 775 780 785	2827
CCC ATC TTT GAG ATC CGA ATG TAT GAT GCC CAG CAG CAG CAA GTT GGC Pro Ile Phe Glu Ile Arg Met Tyr Asp Ala Gln Gln Gln Val Gly 790 795 800	2875
ACC AAC AAA TGC CGG GTG AAC AAT GGC GGC TGC AGC AGC CTG TGC TTG Thr Asn Lys Cys Arg Val Asn Asn Gly Gly Cys Ser Ser Leu Cys Leu 805 810 815	2923
GCC ACC CCT GGG AGC CGC CAG TGC GCC TGT GCT GAG GAC CAG GTG TTG Ala Thr Pro Gly Ser Arg Gln Cys Ala Cys Ala Glu Asp Gln Val Leu 820 825 830 835	2971
GAC GCA GAC GGC GTC ACT TGC TTG GCG AAC CCA TCC TAC GTG CCT CCA Asp Ala Asp Gly Val Thr Cys Leu Ala Asn Pro Ser Tyr Val Pro Pro 840 845 850	3019
CCC CAG TGC CAG CCA GGC GAG TTT GCC TGT GCC AAC AGC AGC CGC TGC ATC Pro Gln Cys Gln Pro Gly Glu Phe Ala Cys Ala Asn Ser Arg Cys Ile 855 860 865	3067
CAG GAG CGC TGG AAG TGT GAC GGA GAC AAC GAT TGC CTG GAC AAC AGT Gln Glu Arg Trp Lys Cys Asp Gly Asp Asn Asp Cys Leu Asp Asn Ser 870 875 880	3115
GAT GAG GCC CCA GCC CTC TGC CAT CAG CAC ACC TGC CCC TCG GAC CGA Asp Glu Ala Pro Ala Leu Cys His Gln His Thr Cys Pro Ser Asp Arg 885 890 895	3163
TTC AAG TGC GAG AAC AAC CGG TGC ATC CCC AAC CGC TGG CTC TGC GAC Phe Lys Cys Glu Asn Asn Arg Cys Ile Pro Asn Arg Trp Leu Cys Asp 900 905 910 915	3211

FIG. 8a

GGG GAC AAT GAC TGT GGG AAC AGT GAA GAT GAG TCC AAT GCC ACT TGT Gly Asp Asn Asp Cys Gly Asn Ser Glu Asp Glu Ser Asn Ala Thr Cys 920 925 930	3259
TCA GCC CGC ACC TGC CCC CCC AAC CAG TTC TCC TGT GCC AGT GGC CGC Ser Ala Arg Thr Cys Pro Pro Asn Gln Phe Ser Cys Ala Ser Gly Arg 935 940 945	3307
TGC ATC CCC ATC TCC TGG ACG TGT GAT CTG GAT GAC GAC TGT GGG GAC Cys Ile Pro Ile Ser Trp Thr Cys Asp Leu Asp Asp Asp Cys Gly Asp 950 955 960	3355
CGC TCT GAT GAG TCT GCT TCG TGT GCC TAT CCC ACC TGC TTC CCC CTG Arg Ser Asp Glu Ser Ala Ser Cys Ala Tyr Pro Thr Cys Phe Pro Leu 965 970 975	3403
ACT CAG TTT ACC TGC AAC AAT GGC AGA TGT ATC AAC ATC AAC TGG AGA Thr Gln Phe Thr Cys Asn Asn Gly Arg Cys Ile Asn Ile Asn Trp Arg 980 985 990 995	3451
TGC GAC AAT GAC AAT GAC TGT GGG GAC AAC AGT GAC GAA GCC GGC TGC Cys Asp Asn Asp Asn Asp Cys Gly Asp Asn Ser Asp Glu Ala Gly Cys 1000 1005 1010	3499
AGC CAC TCC TGT TCT AGC ACC CAG TTC AAG TGC AAC AGC GGG CGT TGC Ser His Ser Cys Ser Ser Thr Gln Phe Lys Cys Asn Ser Gly Arg Cys 1015 1020 1025	3547
ATC CCC GAG CAC TGG ACC TGC GAT GGG GAC AAT GAC TGC GGA GAC TAC Ile Pro Glu His Trp Thr Cys Asp Gly Asp Asn Asp Cys Gly Asp Tyr 1030 1035 1040	3595
AGT GAT GAG ACA CAC GCC AAC TGC ACC AAC CAG GCC ACG AGG CCC CCT Ser Asp Glu Thr His Ala Asn Cys Thr Asn Gln Ala Thr Arg Pro Pro 1045 1050 1055	3643
GGT GGC TGC CAC ACT GAT GAG TTC CAG TGC CGG CTG GAT GGA CTA TGC Gly Gly Cys His Thr Asp Glu Phe Gln Cys Arg Leu Asp Gly Leu Cys 1060 1065 1070 1075	3691
ATC CCC CTG CGG TGG CGC TGC GAT GGG GAC ACT GAC TGC ATG GAC TCC Ile Pro Leu Arg Trp Arg Cys Asp Gly Asp Thr Asp Cys Met Asp Ser 1080 1085 1090	3739
AGC GAT GAG AAG AGC TGT GAG GGA GTG ACC CAC GTC TGC GAT CCC AGT Ser Asp Glu Lys Ser Cys Glu Gly Val Thr His Val Cys Asp Pro Ser 1095 1100 1105	3787
GTC AAG TTT GGC TGC AAG GAC TCA GCT CGG TGC ATC AGC AAA GCG TGG Val Lys Phe Gly Cys Lys Asp Ser Ala Arg Cys Ile Ser Lys Ala Trp 1110 1115 1120	3835
GTG TGT GAT GGC GAC AAT GAC TGT GAG GAT AAC TCG GAC GAG GAG AAC Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Asn Ser Asp Glu Glu Asn 1125 1130 1135	3883
TGC GAG TCC CTG GCC TGC AGG CCA CCC TCG CAC CCT TGT GCC AAC AAC Cys Glu Ser Leu Ala Cys Arg Pro Pro Ser His Pro Cys Ala Asn Asn 1140 1145 1150 1155	3931

FIG. 8a

ACC TCA GTC TGC CTG CCC CCT GAC AAG CTG TGT GAT GGC AAC GAC GAC	3979
Thr Ser Val Cys Leu Pro Pro Asp Lys Leu Cys Asp Gly Asn Asp Asp	
1160 1165 1170	
TGT GGC GAC GGC TCA GAT GAG GGC GAG CTC TGC GAC CAG TGC TCT CTG	4027
Cys Gly Asp Gly Ser Asp Glu Gly Glu Leu Cys Asp Gln Cys Ser Leu	
1175 1180 1185	
AAT AAC GGT GGC TGC AGC CAC AAC TGC TCA GTG GCA CCT GGC GAA GGC	4075
Asn Asn Gly Gly Cys Ser His Asn Cys Ser Val Ala Pro Gly Glu Gly	
1190 1195 1200	
ATT GTG TGT TCC TGC CCT CTG GGC ATG GAG CTG GGG CCC GAC AAC CAC	4123
Ile Val Cys Ser Cys Pro Leu Gly Met Glu Leu Gly Pro Asp Asn His	
1205 1210 1215	
ACC TGC CAG ATC CAG AGC TAC TGT GCC AAG CAT CTC AAA TGC AGC CAA	4171
Thr Cys Gln Ile Gln Ser Tyr Cys Ala Lys His Leu Lys Cys Ser Gln	
1220 1225 1230 1235	
AAG TGC GAC CAG AAC AAG TTC AGC GTG AAG TGC TCC TGC TAC GAG GGC	4219
Lys Cys Asp Gln Asn Lys Phe Ser Val Lys Cys Ser Cys Tyr Glu Gly	
1240 1245 1250	
TGG GTC CTG GAA CCT GAC GGC GAG AGC TGC CGC AGC CTG GAC CCC TTC	4267
Trp Val Leu Glu Pro Asp Gly Glu Ser Cys Arg Ser Leu Asp Pro Phe	
1255 1260 1265	
AAG CCG TTC ATC ATT TTC TCC AAC CGC CAT GAA ATC CGG CGC ATC GAT	4315
Lys Pro Phe Ile Ile Phe Ser Asn Arg His Glu Ile Arg Arg Ile Asp	
1270 1275 1280	
CTT CAC AAA GGA GAC TAC AGC GTC CTG GTG CCC GGC CTG CGC AAC ACC	4363
Leu His Lys Gly Asp Tyr Ser Val Leu Val Pro Gly Leu Arg Asn Thr	
1285 1290 1295	
ATC GCC CTG GAC TTC CAC CTC AGC CAG AGC GCC CTC TAC TGG ACC GAC	4411
Ile Ala Leu Asp Phe His Leu Ser Gln Ser Ala Leu Tyr Trp Thr Asp	
1300 1305 1310 1315	
GTG GTG GAG GAC AAG ATC TAC CGC GGG AAG CTG CTG GAC AAC GGA GCC	4459
Val Val Glu Asp Lys Ile Tyr Arg Gly Lys Leu Leu Asp Asn Gly Ala	
1320 1325 1330	
CTG ACT AGT TTC GAG GTG GTG ATT CAG TAT GGC CTG GCC ACA CCC GAG	4507
Leu Thr Ser Phe Glu Val Val Ile Gln Tyr Gly Leu Ala Thr Pro Glu	
1335 1340 1345	
GGC CTG GCT GTA GAC TGG ATT GCA GGC AAC ATC TAC TGG GTG GAG AGT	4555
Gly Leu Ala Val Asp Trp Ile Ala Gly Asn Ile Tyr Trp Val Glu Ser	
1350 1355 1360	
AAC CTG GAT CAG ATC GAG GTG GCC AAG CTG GAT GGG ACC CTC CGG ACC	4603
Asn Leu Asp Gln Ile Glu Val Ala Lys Leu Asp Gly Thr Leu Arg Thr	
1365 1370 1375	
ACC CTG CTG GCC GGT GAC ATT GAG CAC CCA AGG GCA ATC GCA CTG GAT	4651
Thr Leu Leu Ala Gly Asp Ile Glu His Pro Arg Ala Ile Ala Leu Asp	
1380 1385 1390 1395	

CCC CGG GAT GGG ATC CTG TTT TGG ACA GAC TGG GAT GCC AGC CTG CCC Pro Arg Asp Gly Ile Leu Phe Trp Thr Asp Trp Asp Ala Ser Leu Pro 1400 1405 1410	4699
CGC ATT GAG GCA GCC TCC ATG AGT GGG GCT GGG CGC CGC ACC GTG CAC Arg Ile Glu Ala Ala Ser Met Ser Gly Ala Gly Arg Arg Thr Val His 1415 1420 1425	4747
CGG GAG ACC GGC TCT GGG GGC TGG CCC AAC GGG CTC ACC GTG GAC TAC Arg Glu Thr Gly Ser Gly Gly Trp Pro Asn Gly Leu Thr Val Asp Tyr 1430 1435 1440	4795
CTG GAG AAG CGC ATC CTT TGG ATT GAC GCC AGG TCA GAT GCC ATT TAC Leu Glu Lys Arg Ile Leu Trp Ile Asp Ala Arg Ser Asp Ala Ile Tyr 1445 1450 1455	4843
TCA GCC CGT TAC GAC GGC TCT GGC CAC ATG GAG GTG CTT CGG GGA CAC Ser Ala Arg Tyr Asp Gly Ser Gly His Met Glu Val Leu Arg Gly His 1460 1465 1470 1475	4891
GAG TTC CTG TCG CAC CCG TTT GCA GTG ACG CTG TAC GGG GGG GAG GTC Glu Phe Leu Ser His Pro Phe Ala Val Thr Leu Tyr Gly Glu Val 1480 1485 1490	4939
TAC TGG ACT GAC TGG CGA ACA AAC ACA CTG GCT AAG GCC AAC AAG TGG Tyr Trp Thr Asp Trp Arg Thr Asn Thr Leu Ala Lys Ala Asn Lys Trp 1495 1500 1505	4987
ACC GGC CAC AAT GTC ACC GTG GTA CAG AGG ACC AAC ACC CAG CCC TTT Thr Gly His Asn Val Thr Val Val Gln Arg Thr Asn Thr Gln Pro Phe 1510 1515 1520	5035
GAC CTG CAG GTG TAC CAC CCC TCC CGC CAG CCC ATG GCT CCC AAT CCC Asp Leu Gln Val Tyr His Pro Ser Arg Gln Pro Met Ala Pro Asn Pro 1525 1530 1535	5083
TGT GAG GCC AAT GGG GGC CAG GGC CCC TGC TCC CAC CTG TGT CTC ATC Cys Glu Ala Asn Gly Gly Gln Gly Pro Cys Ser His Leu Cys Leu Ile 1540 1545 1550 1555	5131
AAC TAC AAC CGG ACC GTG TCC TGC GCC TGC CCC CAC CTC ATG AAG CTC Asn Tyr Asn Arg Thr Val Ser Cys Ala Cys Pro His Leu Met Lys Leu 1560 1565 1570	5179
CAC AAG GAC AAC ACC ACC TGC TAT GAG TTT AAG AAG TTC CTG CTG TAC His Lys Asp Asn Thr Thr Cys Tyr Glu Phe Lys Lys Phe Leu Leu Tyr 1575 1580 1585	5227
GCA CGT CAG ATG GAG ATC CGA GGT GTG GAC CTG GAT GCT CCC TAC TAC Ala Arg Gln Met Glu Ile Arg Gly Val Asp Leu Asp Ala Pro Tyr Tyr 1590 1595 1600	5275
AAC TAC ATC ATC TCC TTC ACG GTG CCC GAC ATC GAC AAC GTC ACA GTG Asn Tyr Ile Ile Ser Phe Thr Val Pro Asp Ile Asp Asn Val Thr Val 1605 1610 1615	5323
CTA GAC TAC GAT GCC CGC GAG CAG CGT GTG TAC TGG TCT GAC GTG CGG Leu Asp Tyr Asp Ala Arg Glu Gln Arg Val Tyr Trp Ser Asp Val Arg 1620 1625 1630 1635	5371

FIG. 8a

ACA CAG GCC ATC AAG CGG GCC TTC ATC AAC GGC ACA GGC GTG GAG ACA Thr Gln Ala Ile Lys Arg Ala Phe Ile Asn Gly Thr Gly Val Glu Thr 1640 1645 1650	5419
GTC GTC TCT GCA GAC TTG CCA AAT GCC CAC GGG CTG GCT GTG GAC TGG Val Val Ser Ala Asp Leu Pro Asn Ala His Gly Leu Ala Val Asp Trp 1655 1660 1665	5467
GTC TCC CGA AAC CTG TTC TGG ACA AGC TAT GAC ACC AAT AAG AAG CAG Val Ser Arg Asn Leu Phe Trp Thr Ser Tyr Asp Thr Asn Lys Lys Gln 1670 1675 1680	5515
ATC AAT GTG GCC CGG CTG GAT GGC TCC TTC AAG AAC GCA GTG GTG CAG Ile Asn Val Ala Arg Leu Asp Gly Ser Phe Lys Asn Ala Val Val Gln 1685 1690 1695	5563
GGC CTG GAG CAG CCC CAT GGC CTT GTC GTC CAC CCT CTG CGT GGG AAG Gly Leu Glu Gln Pro His Gly Leu Val Val His Pro Leu Arg Gly Lys 1700 1705 1710 1715	5611
CTC TAC TGG ACC GAT GGT GAC AAC ATC AGC ATG GCC AAC ATG GAT GGC Leu Tyr Trp Thr Asp Gly Asp Asn Ile Ser Met Ala Asn Met Asp Gly 1720 1725 1730	5659
AGC AAT CGC ACC CTG CTC TTC AGT GGC CAG AAG GGC CCC GTG GGC CTG Ser Asn Arg Thr Leu Leu Phe Ser Gly Gln Lys Gly Pro Val Gly Leu 1735 1740 1745	5707
GCT ATT GAC TTC CCT GAA AGC AAA CTC TAC TGG ATC AGC TCC GGG AAC Ala Ile Asp Phe Pro Glu Ser Lys Leu Tyr Trp Ile Ser Ser Gly Asn 1750 1755 1760	5755
CAT ACC ATC AAC CGC TGC AAC CTG GAT GGG AGT GGG CTG GAG GTC ATC His Thr Ile Asn Arg Cys Asn Leu Asp Gly Ser Gly Leu Glu Val Ile 1765 1770 1775	5803
GAT GCC ATG CGG AGC CAG CTG GGC AAG GCC ACC GGC CTG GCC ATC ATG Asp Ala Met Arg Ser Gln Leu Gly Lys Ala Thr Ala Leu Ala Ile Met 1780 1785 1790 1795	5851
GGG GAC AAG CTG TGG TGG GCT GAT CAG GTG TCG GAA AAG ATG GGC ACA Gly Asp Lys Leu Trp Trp Ala Asp Gln Val Ser Glu Lys Met Gly Thr 1800 1805 1810	5899
TGC AGC AAG GCT GAC GGC TCG GGC TCC GTG GTC CTT CGG AAC AGC ACC Cys Ser Lys Ala Asp Gly Ser Gly Ser Val Val Leu Arg Asn Ser Thr 1815 1820 1825	5947
ACC CTG GTG ATG CAC ATG AAG GTC TAT GAC GAG AGC ATC CAG CTG GAC Thr Leu Val Met His Met Lys Val Tyr Asp Glu Ser Ile Gln Leu Asp 1830 1835 1840	5995
CAT AAG GGC ACC AAC CCC TGC AGT GTC AAC AAC GGT GAC TGC TCC CAG His Lys Gly Thr Asn Pro Cys Ser Val Asn Asn Gly Asp Cys Ser Gln 1845 1850 1855	6043
CTC TGC CTG CCC ACG TCA GAG ACG ACC CGC TCC TGC ATG TGC ACA GCC Leu Cys Leu Pro Thr Ser Glu Thr Thr Arg Ser Cys Met Cys Thr Ala 1860 1865 1870 1875	6091

GGC TAT AGC CTC CGG AGT GGC CAG CAG GCC TGC GAG GGC GTA GGT TCC Gly Tyr Ser Leu Arg Ser Gly Gln Gln Ala Cys Glu Gly Val Gly Ser 1880 1885 1890	6139
TTT CTC CTG TAC TCT GTG CAT GAG GGA ATC AGG GGA ATT CCC CTG GAT Phe Leu Leu Tyr Ser Val His Glu Gly Ile Arg Gly Ile Pro Leu Asp 1895 1900 1905	6187
CCC AAT GAC AAG TCA GAT GCC CTG GTC CCA GTG TCC GGG ACC TCG CTG Pro Asn Asp Lys Ser Asp Ala Leu Val Pro Val Ser Gly Thr Ser Leu 1910 1915 1920	6235
GCT GTC GGC ATC GAC TTC CAC GCT GAA AAT GAC ACC ATC TAC TGG GTG Ala Val Gly Ile Asp Phe His Ala Glu Asn Asp Thr Ile Tyr Trp Val 1925 1930 1935	6283
GAC ATG GGC CTG AGC ACG ATC AGC CGG GCC AAG CGG GAC CAG ACG TGG Asp Met Gly Leu Ser Thr Ile Ser Arg Ala Lys Arg Asp Gln Thr Trp 1940 1945 1950 1955	6331
CGT GAA GAC GTG GTG ACC AAT GGC ATT GGC CGT GTG GAG GGC ATT GCA Arg Glu Asp Val Val Thr Asn Gly Ile Gly Arg Val Glu Gly Ile Ala 1960 1965 1970	6379
GTG GAC TGG ATC GCA GGC AAC ATC TAC TGG ACA GAC CAG GGC TTT GAT Val Asp Trp Ile Ala Gly Asn Ile Tyr Trp Thr Asp Gln Gly Phe Asp 1975 1980 1985	6427
GTC ATC GAG GTC GCC CGG CTC AAT GGC TCC TTC CGC TAC GTG GTG ATC Val Ile Glu Val Ala Arg Leu Asn Gly Ser Phe Arg Tyr Val Val Ile 1990 1995 2000	6475
TCC CAG GGT CTA GAC AAG CCC CGG GCC ATC ACC GTC CAC CCG GAG AAA Ser Gln Gly Leu Asp Lys Pro Arg Ala Ile Thr Val His Pro Glu Lys 2005 2010 2015	6523
GGG TAC TTG TTC TGG ACT GAG TGG GGT CAG TAT CCG CGT ATT GAG CGG Gly Tyr Leu Phe Trp Thr Glu Trp Gly Gln Tyr Pro Arg Ile Glu Arg 2020 2025 2030 2035	6571
TCT CGG CTA GAT GGC ACG GAG CGT GTG GTG CTG GTC AAC GTC AGC ATC Ser Arg Leu Asp Gly Thr Glu Arg Val Val Leu Val Asn Val Ser Ile 2040 2045 2050	6619
AGC TGG CCC AAC GGC ATC TCA GTG GAC TAC CAG GAT GGG AAG CTG TAC Ser Trp Pro Asn Gly Ile Ser Val Asp Tyr Gln Asp Gly Lys Leu Tyr 2055 2060 2065	6667
TGG TGC GAT GCA CGG ACA GAC AAG ATT GAA CGG ATC GAC CTG GAG ACA Trp Cys Asp Ala Arg Thr Asp Lys Ile Glu Arg Ile Asp Leu Glu Thr 2070 2075 2080	6715
GGT GAG AAC CGC GAG GTG GTT CTG TCC AGC AAC AAC ATG GAC ATG TTT Gly Glu Asn Arg Glu Val Val Leu Ser Ser Asn Asn Met Asp Met Phe 2085 2090 2095	6763
TCA GTG TCT GTG TTT GAG GAT TTC ATC TAC TGG AGT GAC AGG ACT CAT Ser Val Ser Val Phe Glu Asp Phe Ile Tyr Trp Ser Asp Arg Thr His 2100 2105 2110 2115	6811

GCC AAC GGC TCT ATC AAG CGC GGG AGC AAA GAC AAT GCC ACA GAC TCC Ala Asn Gly Ser Ile Lys Arg Gly Ser Lys Asp Asn Ala Thr Asp Ser 2120 2125 2130	6859
GTG CCC CTG CGA ACC GGC ATC GGC GTC CAG CTT AAA GAC ATC AAA GTC Val Pro Leu Arg Thr Gly Ile Gly Val Gln Leu Lys Asp Ile Lys Val 2135 2140 2145	6907
TTC AAC CGG GAC CGG CAG AAA GGC ACC AAC GTG TGC GCG GTG GCC AAT Phe Asn Arg Asp Arg Gln Lys Gly Thr Asn Val Cys Ala Val Ala Asn 2150 2155 2160	6955
GGC GGG TGC CAG CAG CTG TGC CTG TAC CCG GGC CGT GGG CAG CGG GCC Gly Gly Cys Gln Gln Leu Cys Leu Tyr Arg Gly Arg Gly Gln Arg Ala 2165 2170 2175	7003
TGC GCC TGT GCC CAC GGG ATG CTG GCT GAA GAC GGA GCA TCG TGC CGC Cys Ala Cys Ala His Gly Met Leu Ala Glu Asp Gly Ala Ser Cys Arg 2180 2185 2190 2195	7051
GAG TAT GCC GGC TAC CTG CTC TAC TCA GAG CGC ACC ATT CTC AAG AGT Glu Tyr Ala Gly Tyr Leu Leu Tyr Ser Glu Arg Thr Ile Leu Lys Ser 2200 2205 2210	7099
ATC CAC CTG TCG GAT GAG CGC AAC CTC AAT GCG CCC GTG CAG CCC TTC Ile His Leu Ser Asp Glu Arg Asn Leu Asn Ala Pro Val Gln Pro Phe 2215 2220 2225	7147
GAG GAC CCT GAG CAC ATG AAG AAC GTC ATC GCC CTG GCC TTT GAC TAC Glu Asp Pro Glu His Met Lys Asn Val Ile Ala Leu Ala Phe Asp Tyr 2230 2235 2240	7195
CGG GCA GGC ACC TCT CCG GGC ACC CCC AAT CGC ATC TTC TTC AGC GAC Arg Ala Gly Thr Ser Pro Gly Thr Pro Asn Arg Ile Phe Phe Ser Asp 2245 2250 2255	7243
ATC CAC TTT GGG AAC ATC CAA CAG ATC AAC GAC GAT GGC TCC AGG AGG Ile His Phe Gly Asn Ile Gln Gln Ile Asn Asp Asp Gly Ser Arg Arg 2260 2265 2270 2275	7291
ATC ACC ATT GTG GAA AAC GTG GGC TCC GTG GAA GGC CTG GCC TAT CAC Ile Thr Ile Val Glu Asn Val Gly Ser Val Glu Gly Leu Ala Tyr His 2280 2285 2290	7339
CGT GGC TGG GAC ACT CTC TAT TGG ACA AGC TAC ACG ACA TCC ACC ATC Arg Gly Trp Asp Thr Leu Tyr Trp Thr Ser Tyr Thr Ser Thr Ile 2295 2300 2305	7387
ACG CGC CAC ACA GTG GAC CAG ACC CGC CCA GGG GCC TTC GAG CGT GAG Thr Arg His Thr Val Asp Gln Thr Arg Pro Gly Ala Phe Glu Arg Glu 2310 2315 2320	7435
ACC GTC ATC ACT ATG TCT GGA GAT GAC CAC CCA CGG GCC TTC GTT TTG Thr Val Ile Thr Met Ser Gly Asp Asp His Pro Arg Ala Phe Val Leu 2325 2330 2335	7483
GAC GAG TGC CAG AAC CTC ATG TTC TGG ACC AAC TGG AAT GAG CAG CAT Asp Glu Cys Gln Asn Leu Met Phe Trp Thr Asn Trp Asn Glu Gln His 2340 2345 2350 2355	7531

FIG. 8a

CCC AGC ATC ATG CGG GCG CTC TCG GGA GCC AAT GTC CTG ACC CTT Pro Ser Ile Met Arg Ala Ala Leu Ser Gly Ala Asn Val Leu Thr Leu 2360 2365 2370	7579
ATC GAG AAG GAC ATC CGT ACC CCC AAT GGC CTG GCC ATC GAC CAC CGT Ile Glu Lys Asp Ile Arg Thr Pro Asn Gly Leu Ala Ile Asp His Arg 2375 2380 2385	7627
GCC GAG AAG CTC TAC TTC TCT GAC GCC ACC CTG GAC AAG ATC GAG CGG Ala Glu Lys Leu Tyr Phe Ser Asp Ala Thr Leu Asp Lys Ile Glu Arg 2390 2395 2400	7675
TGC GAG TAT GAC GGC TCC CAC CGC TAT GTG ATC CTA AAG TCA GAG CCT Cys Glu Tyr Asp Gly Ser His Arg Tyr Val Ile Leu Lys Ser Glu Pro 2405 2410 2415	7723
GTC CAC CCC TTC GGG CTG GCC GTG TAT GGG GAG CAC ATT TTC TGG ACT Val His Pro Phe Gly Leu Ala Val Tyr Gly Glu His Ile Phe Trp Thr 2420 2425 2430 2435	7771
GAC TGG GTG CGG CGG GCA GTG CAG CGG GCC AAC AAG CAC GTG GGC AGC Asp Trp Val Arg Arg Ala Val Gln Arg Ala Asn Lys His Val Gly Ser 2440 2445 2450	7819
AAC ATG AAG CTG CTG CGC GTG GAC ATC CCC CAG CAG CCC ATG GGC ATC Asn Met Lys Leu Leu Arg Val Asp Ile Pro Gln Gln Pro Met Gly Ile 2455 2460 2465	7867
ATC GCC GTG GCC AAC GAC ACC AAC AGC TGT GAA CTC TCT CCA TGC CGA Ile Ala Val Ala Asn Asp Thr Asn Ser Cys Glu Leu Ser Pro Cys Arg 2470 2475 2480	7915
ATC AAC AAC GGT GGC TGC CAG GAC CTG TGT CTG CTC ACT CAC CAG GGC Ile Asn Asn Gly Gly Cys Gln Asp Leu Cys Leu Leu Thr His Gln Gly 2485 2490 2495	7963
CAT GTC AAC TGC TCA TGC CGA GGG GGC CGA ATC CTC CAG GAT GAC CTC His Val Asn Cys Ser Cys Arg Gly Arg Ile Leu Gln Asp Asp Leu 2500 2505 2510 2515	8011
ACC TGC CGA GCG GTG AAT TCC TCT TGC CGA GCA CAA GAT GAG TTT GAG Thr Cys Arg Ala Val Asn Ser Ser Cys Arg Ala Gln Asp Glu Phe Glu 2520 2525 2530	8059
TGT GCC AAT GGC GAG TGC ATC AAC TTC AGC CTG ACC TGC GAC GGC GTC Cys Ala Asn Gly Glu Cys Ile Asn Phe Ser Leu Thr Cys Asp Gly Val 2535 2540 2545	8107
CCC CAC TGC AAG GAC AAG TCC GAT GAG AAG CCA TCC TAC TGC AAC TCC Pro His Cys Lys Asp Lys Ser Asp Glu Lys Pro Ser Tyr Cys Asn Ser 2550 2555 2560	8155
CGC CGC TGC AAG AAG ACT TTC CGG CAG TGC AGC AAT GGG CGC TGT GTG Arg Arg Cys Lys Lys Thr Phe Arg Gln Cys Ser Asn Gly Arg Cys Val 2565 2570 2575	8203
TCC AAC ATG CTG TGG TGC AAC GGG GCC GAC GAC TGT GGG GAT GGC TCT Ser Asn Met Leu Trp Cys Asn Gly Ala Asp Asp Cys Gly Asp Gly Ser 2580 2585 2590 2595	8251

FIG. 8a

GAC GAG ATC CCT TGC AAC AAG ACA GCC TGT GGT GTG GGC GAG TTC CGC Asp Glu Ile Pro Cys Asn Lys Thr Ala Cys Gly Val Gly Glu Phe Arg 2600 2605 2610	8299
TGC CGG GAC GGG ACC TGC ATC GGG AAC TCC AGC CGC TGC AAC CAG TTT Cys Arg Asp Gly Thr Cys Ile Gly Asn Ser Ser Arg Cys Asn Gln Phe 2615 2620 2625	8347
GTG GAT TGT GAG GAC GCC TCA GAT GAG ATG AAC TGC AGT GCC ACC GAC Val Asp Cys Glu Asp Ala Ser Asp Glu Met Asn Cys Ser Ala Thr Asp 2630 2635 2640	8395
TGC AGC AGC TAC TTC CGC CTG GGC GTG AAG GGC GTG CTC TTC CAG CCC Cys Ser Ser Tyr Phe Arg Leu Gly Val Lys Gly Val Leu Phe Gln Pro 2645 2650 2655	8443
TGC GAG CGG ACC TCA CTC TGC TAC GCA CCC AGC TGG GTG TGT GAT GGC Cys Glu Arg Thr Ser Leu Cys Tyr Ala Pro Ser Trp Val Cys Asp Gly 2660 2665 2670 2675	8491
GCC AAT GAC TGT GGG GAC TAC AGT GAT GAG CGC GAC TGC CCA GGT GTG Ala Asn Asp Cys Gly Asp Tyr Ser Asp Glu Arg Asp Cys Pro Gly Val 2680 2685 2690	8539
AAA CGC CCC AGA TGC CCT CTG AAT TAC TTC GCC TGC CCT AGT GGG CGC Lys Arg Pro Arg Cys Pro Leu Asn Tyr Phe Ala Cys Pro Ser Gly Arg 2695 2700 2705	8587
TGC ATC CCC ATG AGC TGG ACG TGT GAC AAA GAG GAT GAC TGT GAA CAT Cys Ile Pro Met Ser Trp Thr Cys Asp Lys Glu Asp Asp Cys Glu His 2710 2715 2720	8635
GGC GAG GAC GAG ACC CAC TGC AAC AAG TTC TGC TCA GAG GCC CAG TTT Gly Glu Asp Glu Thr His Cys Asn Lys Phe Cys Ser Glu Ala Gln Phe 2725 2730 2735	8683
GAG TGC CAG AAC CAT CGC TGC ATC TCC AAG CAG TGG CTG TGT GAC GGC Glu Cys Gln Asn His Arg Cys Ile Ser Lys Gln Trp Leu Cys Asp Gly 2740 2745 2750 2755	8731
AGC GAT GAC TGT GGG GAT GGC TCA GAC GAG GCT GCT CAC TGT GAA GGC Ser Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ala His Cys Glu Gly 2760 2765 2770	8779
AAG ACG TGC GGC CCC TCC TCC TTC TCC TGC CCT GGC ACC CAC GTG TGC Lys Thr Cys Gly Pro Ser Ser Phe Ser Cys Pro Gly Thr His Val Cys 2775 2780 2785	8827
GTC CCC GAG CGC TGG CTC TGT GAC GGT GAC AAA GAC TGT GCT GAT GGT Val Pro Glu Arg Trp Leu Cys Asp Gly Asp Lys Asp Cys Ala Asp Gly 2790 2795 2800	8875
GCA GAC GAG AGC ATC GCA GCT GGT TGC TTG TAC AAC AGC ACT TGT GAC Ala Asp Glu Ser Ile Ala Ala Gly Cys Leu Tyr Asn Ser Thr Cys Asp 2805 2810 2815	8923
GAC CGT GAG TTC ATG TGC CAG AAC CGC CAG TGC ATC CCC AAG CAC TTC Asp Arg Glu Phe Met Cys Gln Asn Arg Gln Cys Ile Pro Lys His Phe 2820 2825 2830 2835	8971

FIG. 8a

GTG TGT GAC CAC GAC CGT GAC TGT GCA GAT GGC TCT GAT GAG TCC CCC Val Cys Asp His Asp Arg Asp Cys Ala Asp Gly Ser Asp Glu Ser Pro 2840 2845 2850	9019
GAG TGT GAG TAC CCG ACC TGC GGC CCC AGT GAG TTC CGC TGT GCC AAT Glu Cys Glu Tyr Pro Thr Cys Gly Pro Ser Glu Phe Arg Cys Ala Asn 2855 2860 2865	9067
GGG CGC TGT CTG AGC TCC CGC CAG TGG GAG TGT GAT GGC GAG AAT GAC Gly Arg Cys Leu Ser Ser Arg Gln Trp Glu Cys Asp Gly Glu Asn Asp 2870 2875 2880	9115
TGC CAC GAC CAG AGT GAC GAG GCT CCC AAG AAC CCA CAC TGC ACC AGC Cys His Asp Gln Ser Asp Glu Ala Pro Lys Asn Pro His Cys Thr Ser 2885 2890 2895	9163
CCA GAG CAC AAG TGC AAT GCC TCG TCA CAG TTC CTG TGC AGC AGT GGG Pro Glu His Lys Cys Asn Ala Ser Ser Gln Phe Leu Cys Ser Ser Gly 2900 2905 2910 2915	9211
CGC TGT GTG GCT GAG GCA CTG CTC TGC AAC GGC CAG GAT GAC TGT GGC Arg Cys Val Ala Glu Ala Leu Leu Cys Asn Gly Gln Asp Asp Cys Gly 2920 2925 2930	9259
GAC AGC TCG GAC GAG CGT GGC TGC CAC ATC AAT GAG TGT CTC AGC CGC Asp Ser Ser Asp Glu Arg Gly Cys His Ile Asn Glu Cys Leu Ser Arg 2935 2940 2945	9307
AAG CTC AGT GGC TGC AGC CAG GAC TGT GAG GAC CTC AAG ATC GGC TTC Lys Leu Ser Gly Cys Ser Gln Asp Cys Glu Asp Leu Lys Ile Gly Phe 2950 2955 2960	9355
AAG TGC CGC TGT CGC CCT GGC TTC CGG CTG AAG GAT GAC GGC CGG ACG Lys Cys Arg Cys Arg Pro Gly Phe Arg Leu Lys Asp Asp Gly Arg Thr 2965 2970 2975	9403
TGT GCT GAT GTG GAC GAG TGC AGC ACC ACC TTC CCC TGC AGC CAG CGC Cys Ala Asp Val Asp Glu Cys Ser Thr Thr Phe Pro Cys Ser Gln Arg 2980 2985 2990 2995	9451
TGC ATC AAC ACC CAT GGC AGC TAT AAG TGT CTG TGT GTG GAG GGC TAT Cys Ile Asn Thr His Gly Ser Tyr Lys Cys Leu Cys Val Glu Gly Tyr 3000 3005 3010	9499
GCA CCC CGC GGC GGC GAC CCC CAC AGC TGC AAG GCT GTG ACT GAC GAG Ala Pro Arg Gly Gly Asp Pro His Ser Cys Lys Ala Val Thr Asp Glu 3015 3020 3025	9547
GAA CCG TTT CTG ATC TTC GCC AAC CGG TAC TAC CTG CGC AAG CTC AAC Glu Pro Phe Leu Ile Phe Ala Asn Arg Tyr Tyr Leu Arg Lys Leu Asn 3030 3035 3040	9595
CTG GAC GGG TCC AAC TAC ACG TTA CTT AAG CAG GGC CTG AAC AAC GCC Leu Asp Gly Ser Asn Tyr Thr Leu Leu Lys Gln Gly Leu Asn Asn Ala 3045 3050 3055	9643
GTT GCC TTG GAT TTT GAC TAC CGA GAG CAG ATG ATC TAC TGG ACA GAT Val Ala Leu Asp Phe Asp Tyr Arg Glu Gln Met Ile Tyr Trp Thr Asp 3060 3065 3070 3075	9691

FIG. 8a

GTG ACC ACC CAG GGC AGC ATG ATC CGA AGG ATG CAC CTT AAC GGG AGC Val Thr Thr Gln Gly Ser Met Ile Arg Arg Met His Leu Asn Gly Ser 3080 3085 3090	9739
AAT GTG CAG GTC CTA CAC CGT ACA GGC CTC AGC AAC CCC GAT GGG CTG Asn Val Gln Val Leu His Arg Thr Gly Leu Ser Asn Pro Asp Gly Leu 3095 3100 3105	9787
GCT GTG GAC TGG GTG GGT GGC AAC CTG TAC TGG TGC GAC AAA GGC CGG Ala Val Asp Trp Val Gly Gly Asn Leu Tyr Trp Cys Asp Lys Gly Arg 3110 3115 3120	9835
GAC ACC ATC GAG GTG TCC AAG CTC AAT GGG GCC TAT CGG ACG GTG CTG Asp Thr Ile Glu Val Ser Lys Leu Asn Gly Ala Tyr Arg Thr Val Leu 3125 3130 3135	9883
GTC AGC TCT GGC CTC CGT GAG CCC AGG GCT CTG GTG GTG GAT GTG CAG Val Ser Ser Gly Leu Arg Glu Pro Arg Ala Leu Val Val Asp Val Gln 3140 3145 3150 3155	9931
AAT GGG TAC CTG TAC TGG ACA GAC TGG GGT GAC CAT TCA CTG ATC GGC Asn Gly Tyr Leu Tyr Trp Thr Asp Trp Gly Asp His Ser Leu Ile Gly 3160 3165 3170	9979
CGC ATC GGC ATG GAT GGG TCC AGC CGC AGC GTC ATC GTG GAC ACC AAG Arg Ile Gly Met Asp Gly Ser Ser Arg Ser Val Ile Val Asp Thr Lys 3175 3180 3185	10027
ATC ACA TGG CCC AAT GGC CTG ACG CTG GAC TAT GTC ACT GAG CGC ATC Ile Thr Trp Pro Asn Gly Leu Thr Leu Asp Tyr Val Thr Glu Arg Ile 3190 3195 3200	10075
TAC TGG GCC GAC GCC CGC GAG GAC TAC ATT GAA TTT GCC AGC CTG GAT Tyr Trp Ala Asp Ala Arg Glu Asp Tyr Ile Glu Phe Ala Ser Leu Asp 3205 3210 3215	10123
GGC TCC AAT CGC CAC GTT GTG CTG AGC CAG GAC ATC CCG CAC ATC TTT Gly Ser Asn Arg His Val Val Leu Ser Gln Asp Ile Pro His Ile Phe 3220 3225 3230 3235	10171
GCA CTG ACC CTG TTT GAG GAC TAC GTC TAC TGG ACC GAC TGG GAA ACA Ala Leu Thr Leu Phe Glu Asp Tyr Val Tyr Trp Thr Asp Trp Glu Thr 3240 3245 3250	10219
AAG TCC ATT AAC CGA GCC CAC AAG ACC ACG GGC ACC AAC AAA ACG CTC Lys Ser Ile Asn Arg Ala His Lys Thr Thr Gly Thr Asn Lys Thr Leu 3255 3260 3265	10267
CTC ATC AGC ACG CTG CAC CGG CCC ATG GAC CTG CAT GTC TTC CAT GCC Leu Ile Ser Thr Leu His Arg Pro Met Asp Leu His Val Phe His Ala 3270 3275 3280	10315
CTG CGC CAG CCA GAC GTG CCC AAT CAC CCC TGC AAG GTC AAC AAT GGT Leu Arg Gln Pro Asp Val Pro Asn His Pro Cys Lys Val Asn Asn Gly 3285 3290 3295	10363
GGC TGC AGC AAC CTG TGC CTG TCC CCC GGG GGA GGG CAC AAA TGT Gly Cys Ser Asn Leu Cys Leu Leu Ser Pro Gly Gly His Lys Cys 3300 3305 3310 3315	10411

FIG. 8a

GCC TGC CCC ACC AAC TTC TAC CTG GGC AGC GAT GGG CGC ACC TGT GTG Ala Cys Pro Thr Asn Phe Tyr Leu Gly Ser Asp Gly Arg Thr Cys Val 3320 3325 3330	10459
TCC AAC TGC ACG GCT AGC CAG TTT GTA TGC AAG AAC GAC AAG TGC ATC Ser Asn Cys Thr Ala Ser Gln Phe Val Cys Lys Asn Asp Lys Cys Ile 3335 3340 3345	10507
CCC TTC TGG TGG AAG TGT GAC ACC GAG GAC GAC TGC GGG GAC CAC TCA Pro Phe Trp Trp Lys Cys Asp Thr Glu Asp Asp Cys Gly Asp His Ser 3350 3355 3360	10555
GAC GAG CCC CCG GAC TGC CCT GAG TTC AAG TGC CGG CCC GGA CAG TTC Asp Glu Pro Pro Asp Cys Pro Glu Phe Lys Cys Arg Pro Gly Gln Phe 3365 3370 3375	10603
CAG TGC TCC ACA GGT ATC TGC ACA AAC CCT GCC TTC ATC TGC GAT GGC Gln Cys Ser Thr Gly Ile Cys Thr Asn Pro Ala Phe Ile Cys Asp Gly 3380 3385 3390 3395	10651
GAC AAT GAC TGC CAG GAC AAC AGT GAC GAG GCC AAC TGT GAC ATC CAC Asp Asn Asp Cys Gln Asp Asn Ser Asp Glu Ala Asn Cys Asp Ile His 3400 3405 3410	10699
GTC TGC TTG CCC AGT CAG TTC AAA TGC ACC AAC ACC AAC CGC TGT ATT Val Cys Leu Pro Ser Gln Phe Lys Cys Thr Asn Thr Asn Arg Cys Ile 3415 3420 3425	10747
CCC GGC ATC TTC CGC TGC AAT GGG CAG GAC AAC TGC GGA GAT GGG GAG Pro Gly Ile Phe Arg Cys Asn Gly Gln Asp Asn Cys Gly Asp Gly Glu 3430 3435 3440	10795
GAT GAG AGG GAC TGC CCC GAG GTG ACC TGC GCC CCC AAC CAG TTC CAG Asp Glu Arg Asp Cys Pro Glu Val Thr Cys Ala Pro Asn Gln Phe Gln 3445 3450 3455	10843
TGC TCC ATT ACC AAA CGG TGC ATC CCC CGG GTC TGG GTC TGC GAC CGG Cys Ser Ile Thr Lys Arg Cys Ile Pro Arg Val Trp Val Cys Asp Arg 3460 3465 3470 3475	10891
GAC AAT GAC TGT GTG GAT GGC AGT GAT GAG CCC GCC AAC TGC ACC CAG Asp Asn Asp Cys Val Asp Gly Ser Asp Glu Pro Ala Asn Cys Thr Gln 3480 3485 3490	10939
ATG ACC TGT GGT GTG GAC GAG TTC CGC TGC AAG GAT TCG GGC CGC TGC Met Thr Cys Gly Val Asp Glu Phe Arg Cys Lys Asp Ser Gly Arg Cys 3495 3500 3505	10987
ATC CCA GCG CGT TGG AAG TGT GAC GGA GAG GAT GAC TGT GGG GAT GGC Ile Pro Ala Arg Trp Lys Cys Asp Gly Glu Asp Asp Cys Gly Asp Gly 3510 3515 3520	11035
TCG GAT GAG CCC AAG GAA GAG TGT GAT GAA CGC ACC TGT GAG CCA TAC Ser Asp Glu Pro Lys Glu Glu Cys Asp Glu Arg Thr Cys Glu Pro Tyr 3525 3530 3535	11083
CAG TTC CGC TGC AAG AAC AAC CGC TGC GTG CCC GGC CGC TGG CAG TGC Gln Phe Arg Cys Lys Asn Asn Arg Cys Val Pro Gly Arg Trp Gln Cys 3540 3545 3550 3555	11131

FIG. 8a

GAC TAC GAC AAC GAT TGC GGT GAC AAC TCC GAT GAA GAG AGC TGC ACC Asp Tyr Asp Asn Asp Cys Gly Asp Asn Ser Asp Glu Glu Ser Cys Thr 3560 3565 3570	11179
CCT CGG CCC TGC TCC GAG AGT GAG TTC TCC TGT GCC AAC GGC CGC TGC Pro Arg Pro Cys Ser Glu Ser Glu Phe Ser Cys Ala Asn Gly Arg Cys 3575 3580 3585	11227
ATC GCG GGG CGC TGG AAA TGC GAT GGA GAC CAC GAC TGC GCG GAC GGC Ile Ala Gly Arg Trp Lys Cys Asp Gly Asp His Asp Cys Ala Asp Gly 3590 3595 3600	11275
TCG GAC GAG AAA GAC TGC ACC CCC CGC TGT GAC ATG GAC CAG TTC CAG Ser Asp Glu Lys Asp Cys Thr Pro Arg Cys Asp Met Asp Gln Phe Gln 3605 3610 3615	11323
TGC AAG AGC GGC CAC TGC ATC CCC CTG CGC TGG CGC TGT GAC GCA GAC Cys Lys Ser Gly His Cys Ile Pro Leu Arg Trp Arg Cys Asp Ala Asp 3620 3625 3630 3635	11371
GCC GAC TGC ATG GAC GGC AGC GAC GAG GAG GCC TGC GGC ACT GGC GTG Ala Asp Cys Met Asp Gly Ser Asp Glu Glu Ala Cys Gly Thr Gly Val 3640 3645 3650	11419
CGG ACC TGC CCC CTG GAC GAG TTC CAG TGC AAC AAC ACC TTG TGC AAG Arg Thr Cys Pro Leu Asp Glu Phe Gln Cys Asn Asn Thr Leu Cys Lys 3655 3660 3665	11467
CCG CTG GCC TGG AAG TGC GAT GGC GAG GAT GAC TGT GGG GAC AAC TCA Pro Leu Ala Trp Lys Cys Asp Gly Glu Asp Asp Cys Gly Asp Asn Ser 3670 3675 3680	11515
GAT GAG AAC CCC GAG GAG TGT GCC CGG TTC GTG TGC CCT CCC AAC CGG Asp Glu Asn Pro Glu Glu Cys Ala Arg Phe Val Cys Pro Pro Asn Arg 3685 3690 3695	11563
CCC TTC CGT TGC AAG AAT GAC CGC GTC TGT CTG TGG ATC GGG CGC CAA Pro Phe Arg Cys Lys Asn Asp Arg Val Cys Leu Trp Ile Gly Arg Gln 3700 3705 3710 3715	11611
TGC GAT GGC ACG GAC AAC TGT GGG GAT GGG ACT GAT GAA GAG GAC TGT Cys Asp Gly Thr Asp Asn Cys Gly Asp Gly Thr Asp Glu Glu Asp Cys 3720 3725 3730	11659
GAG CCC CCC ACA GCC CAC ACC CAC TGC AAA GAC AAG AAG GAG TTT Glu Pro Pro Thr Ala His Thr His Cys Lys Asp Lys Lys Glu Phe 3735 3740 3745	11707
CTG TGC CGG AAC CAG CGC TGC CTC TCC TCC CTG CGC TGC AAC ATG Leu Cys Arg Asn Gln Arg Cys Leu Ser Ser Leu Arg Cys Asn Met 3750 3755 3760	11755
TTC GAT GAC TGC GGG GAC GGC TCT GAC GAG GAG GAC TGC AGC ATC GAC Phe Asp Asp Cys Gly Asp Gly Ser Asp Glu Glu Asp Cys Ser Ile Asp 3765 3770 3775	11803
CCC AAG CTG ACC AGC TGC GCC ACC AAT GCC AGC ATC TGT GGG GAC GAG Pro Lys Leu Thr Ser Cys Ala Thr Asn Ala Ser Ile Cys Gly Asp Glu 3780 3785 3790 3795	11851

FIG. 8a

GCA CGC TGC GTG CGC ACC GAG AAA GCG GCC TAC TGT GCC TGC CGC TCG Ala Arg Cys Val Arg Thr Glu Lys Ala Ala Tyr Cys Ala Cys Arg Ser 3800	3805	3810	11899	
GGC TTC CAC ACC GTG CCC GGC CAG CCC GGA TGC CAA GAC ATC AAC GAG Gly Phe His Thr Val Pro Gly Gln Pro Gly Cys Gln Asp Ile Asn Glu 3815	3820	3825	11947	
TGC CTG CGC TTC GGC ACC TGC TCC CAG CTC TGC AAC AAC ACC AAG GGC Cys Leu Arg Phe Gly Thr Cys Ser Gln Leu Cys Asn Asn Thr Lys Gly 3830	3835	3840	11995	
GGC CAC CTC TGC AGC TGC GCT CGG AAC TTC ATG AAG ACG CAC AAC ACC Gly His Leu Cys Ser Cys Ala Arg Asn Phe Met Lys Thr His Asn Thr 3845	3850	3855	12043	
TGC AAG GCC GAA GGC TCT GAG TAC CAG GTC CTG TAC ATC GCT GAT GAC Cys Lys Ala Glu Gly Ser Glu Tyr Gln Val Leu Tyr Ile Ala Asp Asp 3860	3865	3870	3875	12091
AAT GAG ATC CGC AGC CTG TTC CCC GGC CAC CCC CAT TCG GCT TAC GAG Asn Glu Ile Arg Ser Leu Phe Pro Gly His Pro His Ser Ala Tyr Glu 3880	3885	3890	12139	
CAG GCA TTC CAG GGT GAC GAG AGT GTC CGC ATT GAT GCT ATG GAT GTC Gln Ala Phe Gln Gly Asp Glu Ser Val Arg Ile Asp Ala Met Asp Val 3895	3900	3905	12187	
CAT GTC AAG GCT GGC CGT GTC TAT TGG ACC AAC TGG CAC ACG GGC ACC His Val Lys Ala Gly Arg Val Tyr Trp Thr Asn Trp His Thr Gly Thr 3910	3915	3920	12235	
ATC TCC TAC CGC AGC CTG CCA CCT GCT GCG CCT CCT ACC ACT TCC AAC Ile Ser Tyr Arg Ser Leu Pro Pro Ala Ala Pro Pro Thr Thr Ser Asn 3925	3930	3935	12283	
CGC CAC CGG CGA CAG ATT GAC CGG GGT GTC ACC CAC CTC AAC ATT TCA Arg His Arg Arg Gln Ile Asp Arg Gly Val Thr His Leu Asn Ile Ser 3940	3945	3950	3955	12331
GGG CTG AAG ATG CCC AGA GGC ATC GCC ATC GAC TGG GTG GCC GGA AAC Gly Leu Lys Met Pro Arg Gly Ile Ala Ile Asp Trp Val Ala Gly Asn 3960	3965	3970	12379	
GTG TAC TGG ACC GAC TCG GGC CGA GAT GTG ATT GAG GTG GCG CAG ATG Val Tyr Trp Thr Asp Ser Gly Arg Asp Val Ile Glu Val Ala Gln Met 3975	3980	3985	12427	
AAG GGC GAG AAC CGC AAG ACG CTC ATC TCG GGC ATG ATT GAC GAG CCC Lys Gly Glu Asn Arg Lys Thr Leu Ile Ser Gly Met Ile Asp Glu Pro 3990	3995	4000	12475	
CAC GCC ATT GTG GTG GAC CCA CTG AGG GGG ACC ATG TAC TGG TCA GAC His Ala Ile Val Val Asp Pro Leu Arg Gly Thr Met Tyr Trp Ser Asp 4005	4010	4015	12523	
TGG GGC AAC CAC CCC AAG ATT GAG ACG GCA GCG ATG GAT GGG ACG CTT Trp Gly Asn His Pro Lys Ile Glu Thr Ala Ala Met Asp Gly Thr Leu 4020	4025	4030	4035	12571

CGG GAG ACA CTG GTG CAG GAC AAC ATT CAG TGG CCC ACA GGC CTG GCC Arg Glu Thr Leu Val Gln Asp Asn Ile Gln Trp Pro Thr Gly Leu Ala 4040 4045 4050	12619
GTG GAT TAT CAC AAT GAG CGG CTG TAC TGG GCA GAC GCC AAG CTT TCA Val Asp Tyr His Asn Glu Arg Leu Tyr Trp Ala Asp Ala Lys Leu Ser 4055 4060 4065	12667
GTC ATC GGC AGC ATC CGG CTC AAT GGC ACG GAC CCC ATT GTG GCT GCT Val Ile Gly Ser Ile Arg Leu Asn Gly Thr Asp Pro Ile Val Ala Ala 4070 4075 4080	12715
GAC AGC AAA CGA GGC CTA AGT CAC CCC TTC AGC ATC GAC GTC TTT GAG Asp Ser Lys Arg Gly Leu Ser His Pro Phe Ser Ile Asp Val Phe Glu 4085 4090 4095	12763
GAT TAC ATC TAT GGT GTC ACC TAC ATC AAT CGT GTC TTC AAG ATC Asp Tyr Ile Tyr Gly Val Thr Tyr Ile Asn Asn Arg Val Phe Lys Ile 4100 4105 4110 4115	12811
CAT AAG TTT GGC CAC AGC CCC TTG GTC AAC CTG ACA GGG GGC CTG AGC His Lys Phe Gly His Ser Pro Leu Val Asn Leu Thr Gly Gly Leu Ser 4120 4125 4130	12859
CAC GCC TCT GAC GTG GTC CTT TAC CAT CAG CAC AAG CAG CCC GAA GTG His Ala Ser Asp Val Val Leu Tyr His Gln His Lys Gln Pro Glu Val 4135 4140 4145	12907
ACC AAC CCA TGT GAC CGC AAG AAA TGC GAG TGG CTC TGC CTG CTG AGC Thr Asn Pro Cys Asp Arg Lys Lys Cys Glu Trp Leu Cys Leu Leu Ser 4150 4155 4160	12955
CCC AGT GGG CCT GTC TGC ACC TGT CCC AAT GGG AAG CGG CTG GAC AAC Pro Ser Gly Pro Val Cys Thr Cys Pro Asn Gly Lys Arg Leu Asp Asn 4165 4170 4175	13003
GGC ACA TGC GTG CCT GTG CCC TCT CCA ACG CCC CCC CCA GAT GCT CCC Gly Thr Cys Val Pro Val Pro Ser Pro Thr Pro Pro Pro Asp Ala Pro 4180 4185 4190 4195	13051
CGG CCT GGA ACC TGT AAC CTG CAG TGC TTC AAC GGT GGC AGC TGT TTC Arg Pro Gly Thr Cys Asn Leu Gln Cys Phe Asn Gly Gly Ser Cys Phe 4200 4205 4210	13099
CTC AAT GCA CGG AGG CAG CCC AAG TGC CGC TGC CAA CCC CGC TAC ACG Leu Asn Ala Arg Arg Gln Pro Lys Cys Arg Cys Gln Pro Arg Tyr Thr 4215 4220 4225	13147
GGT GAC AAG TGT GAA CTG GAC CAG TGC TGG GAG CAC TGT CGC AAT GGG Gly Asp Lys Cys Glu Leu Asp Gln Cys Trp Glu His Cys Arg Asn Gly 4230 4235 4240	13195
GGC ACC TGT GCT GCC TCC CCC TCT GGC ATG CCC ACG TGC CGG TGC CCC Gly Thr Cys Ala Ala Ser Pro Ser Gly Met Pro Thr Cys Arg Cys Pro 4245 4250 4255	13243
ACG GGC TTC ACG GGC CCC AAA TGC ACC CAG CAG GTG TGT GCG GGC TAC Thr Gly Phe Thr Gly Pro Lys Cys Thr Gln Gln Val Cys Ala Gly Tyr 4260 4265 4270 4275	13291

FIG. 8a

TGT GCC AAC AAC AGC ACC TGC ACT GTC AAC CAG GGC AAC CAG CCC CAG Cys Ala Asn Asn Ser Thr Cys Thr Val Asn Gln Gly Asn Gln Pro Gln 4280 4285 4290	13339
TGC CGA TGC CTA CCC GGC TTC CTG GGC GAC CGC TGC CAG TAC CGG CAG Cys Arg Cys Leu Pro Gly Phe Leu Gly Asp Arg Cys Gln Tyr Arg Gln 4295 4300 4305	13387
TGC TCT GGC TAC TGT GAG AAC TTT GGC ACA TGC CAG ATG GCT GCT GAT Cys Ser Gly Tyr Cys Glu Asn Phe Gly Thr Cys Gln Met Ala Ala Asp 4310 4315 4320	13435
GGC TCC CGA CAA TGC CGC TGC ACT GCC TAC TTT GAG GGA TCG AGG TGT Gly Ser Arg Gln Cys Arg Cys Thr Ala Tyr Phe Glu Gly Ser Arg Cys 4325 4330 4335	13483
GAG GTG AAC AAG TGC AGC CGC TGT CTC GAA GGG GCC TGT GTG GTC AAC Glu Val Asn Lys Cys Ser Arg Cys Leu Glu Gly Ala Cys Val Val Asn 4340 4345 4350 4355	13531
AAG CAG AGT GGG GAT GTC ACC TGC AAC TGC ACG GAT GGC CGG GTG GCC Lys Gln Ser Gly Asp Val Thr Cys Asn Cys Thr Asp Gly Arg Val Ala 4360 4365 4370	13579
CCC AGC TGT CTG ACC TGC GTC GGC CAC TGC AGC AAT GGC GGC TCC TGT Pro Ser Cys Leu Thr Cys Val Gly His Cys Ser Asn Gly Ser Cys 4375 4380 4385	13627
ACC ATG AAC AGC AAA ATG ATG CCT GAG TGC CAG TGC CCA CCC CAC ATG Thr Met Asn Ser Lys Met Met Pro Glu Cys Gln Cys Pro Pro His Met 4390 4395 4400	13675
ACA GGG CCC CGG TGT GAG GAG CAC GTC TTC AGC CAG CAG CCA GGA Thr Gly Pro Arg Cys Glu Glu His Val Phe Ser Gln Gln Pro Gly 4405 4410 4415	13723
CAT ATA GCC TCC ATC CTA ATC CCT CTG CTG TTG CTG CTG CTG CTG CTG GTT His Ile Ala Ser Ile Leu Ile Pro Leu Leu Leu Leu Leu Leu Val 4420 4425 4430 4435	13771
CTG GTG GCC GGA GTG GTA TTC TGG TAT AAG CGG CGA GTC CAA GGG GCT Leu Val Ala Gly Val Val Phe Trp Tyr Lys Arg Arg Val Gln Gly Ala 4440 4445 4450	13819
AAG GGC TTC CAG CAC CAA CGG ATG ACC AAC GGG GCC ATG AAC GTG GAG Lys Gly Phe Gln His Gln Arg Met Thr Asn Gly Ala Met Asn Val Glu 4455 4460 4465	13867
ATT GGA AAC CCC ACC TAC AAG ATG TAC GAA GGC GGA GAG CCT GAT GAT Ile Gly Asn Pro Thr Tyr Lys Met Tyr Glu Gly Glu Pro Asp Asp 4470 4475 4480	13915
GTG GGA GGC CTA CTG GAC GCT TTT GCC CTG GAC CCT GAC AAG CCC Val Gly Gly Leu Leu Asp Ala Asp Phe Ala Leu Asp Pro Asp Lys Pro 4485 4490 4495	13963
ACC AAC TTC ACC AAC CCC GTG TAT GCC ACA CTC TAC ATG GGG GGC CAT Thr Asn Phe Thr Asn Pro Val Tyr Ala Thr Leu Tyr Met Gly Gly His 4500 4505 4510 4515	14011

GGC AGT CGC CAC TCC CTG GCC AGC ACG GAC GAG AAG CGA GAA CTC CTG 14059
 Gly Ser Arg His Ser Leu Ala Ser Thr Asp Glu Lys Arg Glu Leu Leu
 4520 4525 4530

GGC CGG GGC CCT GAG GAC GAG ATA GGG GAC CCC TTG GCA TAGGGCCCTG CC 14110
 CCGTCGGACT GCCCCCAGAA AGCCTCTGC CCCCTGCCGG TGAAGTCCTT CAGTGAGCCC 14170
 Gly Arg Gly Pro Glu Asp Glu Ile Gly Asp Pro Leu Ala
 4535 4540

CTCCTTCTCC AGCCCTTCCC TGGCCCCCCC GGATGTATAA ATGTAAAAAT GAAGGAATTA 14230
 CATTCTATAT GTGAGCGAGC AAGCCGGCAA GCGAGCACAG TATTATTTCT CCATCCCCTC 14290
 CCTGCCTGCT CCTTGGCACCC CCCATGCTGC CTCAGGGAG ACAGGCAGGG AGGGCTTGGG 14350
 GCTGCACCTC CTACCCCTCCC ACCAGAACGC ACCCCACTGG GAGAGCTGGT GGTGCAGCCT 14410
 TCCCCCTCCCT GTATAAGACA CTTTGCCAAG GCTCTCCCCCT CTCGCCCCAT CCCTGCTTGC 14470
 CCGCTCCAC AGCTTCCTGA GGGCTAATTC TGGGAAGGGGA GAGTTCTTTG CTGCCCCCTGT 14530
 CTGGAAGACG TGGCTCTGGG TGAGGTAGGC GGGAAAGGGAT GGAGTGTGTT AGTTCTTGGG 14590
 GGAGGCCACC CCAAACCCCA GCCCCAACTC CAGGGGGCACC TATGAGATGG CCATGCTCAA 14650
 CCCCCCTCCCT AGACAGGCC CTCCTGTCTC CAGGGCCCCC ACCGAGGTTC CCAGGGCTGG 14710
 AGACTTCCTC TGGTAAACAT TCCTCCAGCC TCCCCCTCCCC TGGGGACGCC AAGGAGGTGG 14770
 GCCACACCCCA GGAAGGGAAA GCGGGCAGCC CGGTTTGGG GACGTGAACG TTTTAATAAT 14830
 TTTGCTGAA TTCTTACAA CTAAATAACA CAGATATTCT TATAAATAAA ATTGTAAAAA 14890
 AAAAAAA 14896

FIG. 8a

Met	Leu	Thr	Pro	Pro	Leu	Leu	Leu	Leu	Pro	Leu	Leu	Ser	Ala	Leu		
1					5			10				15				
Val	Ala	Ala	Ala	Ile	Asp	Ala	Pro	Lys	Thr	Cys	Ser	Pro	Lys	Gln	Phe	
				20				25				30				
Ala	Cys	Arg	Asp	Gln	Ile	Thr	Cys	Ile	Ser	Lys	Gly	Trp	Arg	Cys	Asp	
				35			40				45					
Gly	Glu	Arg	Asp	Cys	Pro	Asp	Gly	Ser	Asp	Glu	Ala	Pro	Glu	Ile	Cys	
				50			55				60					
Pro	Gln	Ser	Lys	Ala	Gln	Arg	Cys	Gln	Pro	Asn	Glu	His	Asn	Cys	Leu	
				65			70				75			80		
Gly	Thr	Glu	Leu	Cys	Val	Pro	Met	Ser	Arg	Leu	Cys	Asn	Gly	Val	Gln	
				85			90				95					
Asp	Cys	Met	Asp	Gly	Ser	Asp	Glu	Gly	Pro	His	Cys	Arg	Glu	Leu	Gln	
				100			105				110					
Gly	Asn	Cys	Ser	Arg	Leu	Gly	Cys	Gln	His	His	Cys	Val	Pro	Thr	Leu	
				115			120				125					
Asp	Gly	Pro	Thr	Cys	Tyr	Cys	Asn	Ser	Ser	Phe	Gln	Leu	Gln	Ala	Asp	
				130			135				140					
Gly	Lys	Thr	Cys	Lys	Asp	Phe	Asp	Glu	Cys	Ser	Val	Tyr	Gly	Thr	Cys	
				145			150				155			160		
Ser	Gln	Leu	Cys	Thr	Asn	Thr	Asp	Gly	Ser	Phe	Ile	Cys	Gly	Cys	Val	
				165			170				175					
Glu	Gly	Tyr	Leu	Leu	Gln	Pro	Asp	Asn	Arg	Ser	Cys	Lys	Ala	Lys	Asn	
				180			185				190					
Glu	Pro	Val	Asp	Arg	Pro	Pro	Val	Leu	Leu	Ile	Ala	Asn	Ser	Gln	Asn	
				195			200				205					
Ile	Leu	Ala	Thr	Tyr	Leu	Ser	Gly	Ala	Gln	Val	Ser	Thr	Ile	Thr	Pro	
				210			215				220					
Thr	Ser	Thr	Arg	Gln	Thr	Thr	Ala	Met	Asp	Phe	Ser	Tyr	Ala	Asn	Glu	
				225			230				235			240		
Thr	Val	Cys	Trp	Val	His	Val	Gly	Asp	Ser	Ala	Ala	Gln	Thr	Gln	Leu	
				245			250				255					
Lys	Cys	Ala	Arg	Met	Pro	Gly	Leu	Lys	Gly	Phe	Val	Asp	Glu	His	Thr	
				260			265				270					
Ile	Asn	Ile	Ser	Leu	Ser	Leu	His	His	Val	Glu	Gln	Met	Ala	Ile	Asp	
				275			280				285					
Trp	Leu	Thr	Gly	Asn	Phe	Tyr	Phe	Val	Asp	Asp	Ile	Asp	Asp	Arg	Ile	
				290			295				300					
Phe	Val	Cys	Asn	Arg	Asn	Gly	Asp	Thr	Cys	Val	Thr	Leu	Leu	Asp	Leu	
				305			310				315			320		
Glu	Leu	Tyr	Asn	Pro	Lys	Gly	Ile	Ala	Leu	Asp	Pro	Ala	Met	Gly	Lys	
				325			330				335					
Val	Phe	Phe	Thr	Asp	Tyr	Gly	Gln	Ile	Pro	Lys	Val	Glu	Arg	Cys	Asp	
				340			345				350					
Met	Asp	Gly	Gln	Asn	Arg	Thr	Lys	Leu	Val	Asp	Ser	Lys	Ile	Val	Phe	
				355			360				365					
Pro	His	Gly	Ile	Thr	Leu	Asp	Leu	Val	Ser	Arg	Leu	Tyr	Trp	Ala		
				370			375				380					
Asp	Ala	Tyr	Leu	Asp	Tyr	Ile	Glu	Val	Val	Asp	Tyr	Glu	Gly	Lys	Gly	
				385			390				395			400		
Arg	Gln	Thr	Ile	Ile	Gln	Gly	Ile	Leu	Ile	Glu	His	Leu	Tyr	Gly	Leu	
				405			410				415					
Thr	Val	Phe	Glu	Asn	Tyr	Leu	Tyr	Ala	Thr	Asn	Ser	Asp	Asn	Ala	Asn	
				420			425				430					
Ala	Gln	Gln	Lys	Thr	Ser	Val	Ile	Arg	Val	Asn	Arg	Phe	Asn	Ser	Thr	
				435			440				445					
Glu	Tyr	Gln	Val	Val	Val	Thr	Arg	Val	Asp	Lys	Gly	Gly	Ala	Leu	His	Ile
				450			455				460					

FIG. 8b

Tyr His Gln Arg Arg Gln Pro Arg Val Arg Ser His Ala Cys Glu Asn
 465 470 475 480
 Asp Gln Tyr Gly Lys Pro Gly Gly Cys Ser Asp Ile Cys Leu Leu Ala
 485 490 495
 Asn Ser His Lys Ala Arg Thr Cys Arg Cys Arg Ser Gly Phe Ser Leu
 500 505 510
 Gly Ser Asp Gly Lys Ser Cys Lys Lys Pro Glu His Glu Leu Phe Leu
 515 520 525
 Val Tyr Gly Lys Gly Arg Pro Gly Ile Ile Arg Gly Met Asp Met Gly
 530 535 540
 Ala Lys Val Pro Asp Glu His Met Ile Pro Ile Glu Asn Leu Met Asn
 545 550 555 560
 Pro Arg Ala Leu Asp Phe His Ala Glu Thr Gly Phe Ile Tyr Phe Ala
 565 570 575
 Asp Thr Thr Ser Tyr Leu Ile Gly Arg Gln Lys Ile Asp Gly Thr Glu
 580 585 590
 Arg Glu Thr Ile Leu Lys Asp Gly Ile His Asn Val Glu Gly Val Ala
 595 600 605
 Val Asp Trp Met Gly Asp Asn Leu Tyr Trp Thr Asp Asp Gly Pro Lys
 610 615 620
 Lys Thr Ile Ser Val Ala Arg Leu Glu Lys Ala Ala Gln Thr Arg Lys
 625 630 635 640
 Thr Leu Ile Glu Gly Lys Met Thr His Pro Arg Ala Ile Val Val Asp
 645 650 655
 Pro Leu Asn Gly Trp Met Tyr Trp Thr Asp Trp Glu Glu Asp Pro Lys
 660 665 670
 Asp Ser Arg Arg Gly Arg Leu Glu Arg Ala Trp Met Asp Gly Ser His
 675 680 685
 Arg Asp Ile Phe Val Thr Ser Lys Thr Val Leu Trp Pro Asn Gly Leu
 690 695 700
 Ser Leu Asp Ile Pro Ala Gly Arg Leu Tyr Trp Val Asp Ala Phe Tyr
 705 710 715 720
 Asp Arg Ile Glu Thr Ile Leu Leu Asn Gly Thr Asp Arg Lys Ile Val
 725 730 735
 Tyr Glu Gly Pro Glu Leu Asn His Ala Phe Gly Leu Cys His His Gly
 740 745 750
 Asn Tyr Leu Phe Trp Thr Glu Tyr Arg Ser Gly Ser Val Tyr Arg Leu
 755 760 765
 Glu Arg Gly Val Gly Gly Ala Pro Pro Thr Val Thr Leu Leu Arg Ser
 770 775 780
 Glu Arg Pro Pro Ile Phe Glu Ile Arg Met Tyr Asp Ala Gln Gln
 785 790 795 800
 Gln Val Gly Thr Asn Lys Cys Arg Val Asn Asn Gly Gly Cys Ser Ser
 805 810 815
 Leu Cys Leu Ala Thr Pro Gly Ser Arg Gln Cys Ala Cys Ala Glu Asp
 820 825 830
 Gln Val Leu Asp Ala Asp Gly Val Thr Cys Leu Ala Asn Pro Ser Tyr
 835 840 845
 Val Pro Pro Pro Gln Cys Gln Pro Gly Glu Phe Ala Cys Ala Asn Ser
 850 855 860
 Arg Cys Ile Gln Glu Arg Trp Lys Cys Asp Gly Asp Asn Asp Cys Leu
 865 870 875 880
 Asp Asn Ser Asp Glu Ala Pro Ala Leu Cys His Gln His Thr Cys Pro
 885 890 895
 Ser Asp Arg Phe Lys Cys Glu Asn Asn Arg Cys Ile Pro Asn Arg Trp
 900 905 910
 Leu Cys Asp Gly Asp Asn Asp Cys Gly Asn Ser Glu Asp Glu Ser Asn
 915 920 925

FIG. 8b

Ala Thr Cys Ser Ala Arg Thr Cys Pro Pro Asn Gln Phe Ser Cys Ala
 930 935 940
 Ser Gly Arg Cys Ile Pro Ile Ser Trp Thr Cys Asp Leu Asp Asp Asp
 945 950 955 960
 Cys Gly Asp Arg Ser Asp Glu Ser Ala Ser Cys Ala Tyr Pro Thr Cys
 965 970 975
 Phe Pro Leu Thr Gln Phe Thr Cys Asn Asn Gly Arg Cys Ile Asn Ile
 980 985 990
 Asn Trp Arg Cys Asp Asn Asp Asn Cys Gly Asp Asn Ser Asp Glu
 995 1000 1005
 Ala Gly Cys Ser His Ser Cys Ser Ser Thr Gln Phe Lys Cys Asn Ser
 1010 1015 1020
 Gly Arg Cys Ile Pro Glu His Trp Thr Cys Asp Gly Asp Asn Asp Cys
 1025 1030 1035 1040
 Gly Asp Tyr Ser Asp Glu Thr His Ala Asn Cys Thr Asn Gln Ala Thr
 1045 1050 1055
 Arg Pro Pro Gly Cys His Thr Asp Glu Phe Gln Cys Arg Leu Asp
 1060 1065 1070
 Gly Leu Cys Ile Pro Leu Arg Trp Arg Cys Asp Gly Asp Thr Asp Cys
 1075 1080 1085
 Met Asp Ser Ser Asp Glu Lys Ser Cys Glu Gly Val Thr His Val Cys
 1090 1095 1100
 Asp Pro Ser Val Lys Phe Gly Cys Lys Asp Ser Ala Arg Cys Ile Ser
 1105 1110 1115 1120
 Lys Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Asn Ser Asp
 1125 1130 1135
 Glu Glu Asn Cys Glu Ser Leu Ala Cys Arg Pro Pro Ser His Pro Cys
 1140 1145 1150
 Ala Asn Asn Thr Ser Val Cys Leu Pro Pro Asp Lys Leu Cys Asp Gly
 1155 1160 1165
 Asn Asp Asp Cys Gly Asp Gly Ser Asp Glu Gly Glu Leu Cys Asp Gln
 1170 1175 1180
 Cys Ser Leu Asn Asn Gly Gly Cys Ser His Asn Cys Ser Val Ala Pro
 1185 1190 1195 1200
 Gly Glu Gly Ile Val Cys Ser Cys Pro Leu Gly Met Glu Leu Gly Pro
 1205 1210 1215
 Asp Asn His Thr Cys Gln Ile Gln Ser Tyr Cys Ala Lys His Leu Lys
 1220 1225 1230
 Cys Ser Gln Lys Cys Asp Gln Asn Lys Phe Ser Val Lys Cys Ser Cys
 1235 1240 1245
 Tyr Glu Gly Trp Val Leu Glu Pro Asp Gly Glu Ser Cys Arg Ser Leu
 1250 1255 1260
 Asp Pro Phe Lys Pro Phe Ile Ile Phe Ser Asn Arg His Glu Ile Arg
 1265 1270 1275 1280
 Arg Ile Asp Leu His Lys Gly Asp Tyr Ser Val Leu Val Pro Gly Leu
 1285 1290 1295
 Arg Asn Thr Ile Ala Leu Asp Phe His Leu Ser Gln Ser Ala Leu Tyr
 1300 1305 1310
 Trp Thr Asp Val Val Glu Asp Lys Ile Tyr Arg Gly Lys Leu Leu Asp
 1315 1320 1325
 Asn Gly Ala Leu Thr Ser Phe Glu Val Val Ile Gln Tyr Gly Leu Ala
 1330 1335 1340
 Thr Pro Glu Gly Leu Ala Val Asp Trp Ile Ala Gly Asn Ile Tyr Trp
 1345 1350 1355 1360
 Val Glu Ser Asn Leu Asp Gln Ile Glu Val Ala Lys Leu Asp Gly Thr
 1365 1370 1375
 Leu Arg Thr Thr Leu Leu Ala Gly Asp Ile Glu His Pro Arg Ala Ile
 1380 1385 1390

- FIG. 8b

Ala Leu Asp Pro Arg Asp Gly Ile Leu Phe Trp Thr Asp Trp Asp Ala
 1395 1400 1405
 Ser Leu Pro Arg Ile Glu Ala Ala Ser Met Ser Gly Ala Gly Arg Arg
 1410 1415 1420
 Thr Val His Arg Glu Thr Gly Ser Gly Gly Trp Pro Asn Gly Leu Thr
 425 1430 1435 1440
 Val Asp Tyr Leu Glu Lys Arg Ile Leu Trp Ile Asp Ala Arg Ser Asp
 1445 1450 1455
 Ala Ile Tyr Ser Ala Arg Tyr Asp Gly Ser Gly His Met Glu Val Leu
 1460 1465 1470
 Arg Gly His Glu Phe Leu Ser His Pro Phe Ala Val Thr Leu Tyr Gly
 1475 1480 1485
 Gly Glu Val Tyr Trp Thr Asp Trp Arg Thr Asn Thr Leu Ala Lys Ala
 1490 1495 1500
 Asn Lys Trp Thr Gly His Asn Val Thr Val Val Gln Arg Thr Asn Thr
 505 1510 1515 1520
 Gln Pro Phe Asp Leu Gln Val Tyr His Pro Ser Arg Gln Pro Met Ala
 1525 1530 1535
 Pro Asn Pro Cys Glu Ala Asn Gly Gly Gln Gly Pro Cys Ser His Leu
 1540 1545 1550
 Cys Leu Ile Asn Tyr Asn Arg Thr Val Ser Cys Ala Cys Pro His Leu
 1555 1560 1565
 Met Lys Leu His Lys Asp Asn Thr Thr Cys Tyr Glu Phe Lys Lys Phe
 1570 1575 1580
 Leu Leu Tyr Ala Arg Gln Met Glu Ile Arg Gly Val Asp Leu Asp Ala
 585 1590 1595 1600
 Pro Tyr Tyr Asn Tyr Ile Ile Ser Phe Thr Val Pro Asp Ile Asp Asn
 1605 1610 1615
 Val Thr Val Leu Asp Tyr Asp Ala Arg Glu Gln Arg Val Tyr Trp Ser
 1620 1625 1630
 Asp Val Arg Thr Gln Ala Ile Lys Arg Ala Phe Ile Asn Gly Thr Gly
 1635 1640 1645
 Val Glu Thr Val Val Ser Ala Asp Leu Pro Asn Ala His Gly Leu Ala
 1650 1655 1660
 Val Asp Trp Val Ser Arg Asn Leu Phe Trp Thr Ser Tyr Asp Thr Asn
 665 1670 1675 1680
 Lys Lys Gln Ile Asn Val Ala Arg Leu Asp Gly Ser Phe Lys Asn Ala
 1685 1690 1695
 Val Val Gln Gly Leu Glu Gln Pro His Gly Leu Val Val His Pro Leu
 1700 1705 1710
 Arg Gly Lys Leu Tyr Trp Thr Asp Gly Asp Asn Ile Ser Met Ala Asn
 1715 1720 1725
 Met Asp Gly Ser Asn Arg Thr Leu Leu Phe Ser Gly Gln Lys Gly Pro
 1730 1735 1740
 Val Gly Leu Ala Ile Asp Phe Pro Glu Ser Lys Leu Tyr Trp Ile Ser
 745 1750 1755 1760
 Ser Gly Asn His Thr Ile Asn Arg Cys Asn Leu Asp Gly Ser Gly Leu
 1765 1770 1775
 Glu Val Ile Asp Ala Met Arg Ser Gln Leu Gly Lys Ala Thr Ala Leu
 1780 1785 1790
 Ala Ile Met Gly Asp Lys Leu Trp Trp Ala Asp Gln Val Ser Glu Lys
 1795 1800 1805
 Met Gly Thr Cys Ser Lys Ala Asp Gly Ser Gly Ser Val Val Leu Arg
 1810 1815 1820
 Asn Ser Thr Thr Leu Val Met His Met Lys Val Tyr Asp Glu Ser Ile
 825 1830 1835 1840
 Gln Leu Asp His Lys Gly Thr Asn Pro Cys Ser Val Asn Asn Gly Asp
 1845 1850 1855
 Cys Ser Gln Leu Cys Leu Pro Thr Ser Glu Thr Thr Arg Ser Cys Met

FIG. 8b

1860	1865	1870
Cys Thr Ala Gly Tyr Ser Leu Arg Ser Gly Gln Gln Ala Cys Glu Gly		
1875	1880	1885
Val Gly Ser Phe Leu Leu Tyr Ser Val His Glu Gly Ile Arg Gly Ile		
1890	1895	1900
Pro Leu Asp Pro Asn Asp Lys Ser Asp Ala Leu Val Pro Val Ser Gly		
905	1910	1915
Thr Ser Leu Ala Val Gly Ile Asp Phe His Ala Glu Asn Asp Thr Ile		
1925	1930	1935
Tyr Trp Val Asp Met Gly Leu Ser Thr Ile Ser Arg Ala Lys Arg Asp		
1940	1945	1950
Gln Thr Trp Arg Glu Asp Val Val Thr Asn Gly Ile Gly Arg Val Glu		
1955	1960	1965
Gly Ile Ala Val Asp Trp Ile Ala Gly Asn Ile Tyr Trp Thr Asp Gln		
1970	1975	1980
Gly Phe Asp Val Ile Glu Val Ala Arg Leu Asn Gly Ser Phe Arg Tyr		
985	1990	1995
2000		
Val Val Ile Ser Gln Gly Leu Asp Lys Pro Arg Ala Ile Thr Val His		
2005	2010	2015
Pro Glu Lys Gly Tyr Leu Phe Trp Thr Glu Trp Gly Gln Tyr Pro Arg		
2020	2025	2030
Ile Glu Arg Ser Arg Leu Asp Gly Thr Glu Arg Val Val Leu Val Asn		
2035	2040	2045
Val Ser Ile Ser Trp Pro Asn Gly Ile Ser Val Asp Tyr Gln Asp Gly		
2050	2055	2060
Lys Leu Tyr Trp Cys Asp Ala Arg Thr Asp Lys Ile Glu Arg Ile Asp		
065	2070	2075
2080		
Leu Glu Thr Gly Glu Asn Arg Glu Val Val Leu Ser Ser Asn Asn Met		
2085	2090	2095
Asp Met Phe Ser Val Ser Val Phe Glu Asp Phe Ile Tyr Trp Ser Asp		
2100	2105	2110
Arg Thr His Ala Asn Gly Ser Ile Lys Arg Gly Ser Lys Asp Asn Ala		
2115	2120	2125
Thr Asp Ser Val Pro Leu Arg Thr Gly Ile Gly Val Gln Leu Lys Asp		
2130	2135	2140
Ile Lys Val Phe Asn Arg Asp Arg Gln Lys Gly Thr Asn Val Cys Ala		
145	2150	2155
2160		
Val Ala Asn Gly Gly Cys Gln Gln Leu Cys Leu Tyr Arg Gly Arg Gly		
2165	2170	2175
Gln Arg Ala Cys Ala Cys Ala His Gly Met Leu Ala Glu Asp Gly Ala		
2180	2185	2190
Ser Cys Arg Glu Tyr Ala Gly Tyr Leu Leu Tyr Ser Glu Arg Thr Ile		
2195	2200	2205
Leu Lys Ser Ile His Leu Ser Asp Glu Arg Asn Leu Asn Ala Pro Val		
2210	2215	2220
Gln Pro Phe Glu Asp Pro Glu His Met Lys Asn Val Ile Ala Leu Ala		
2225	2230	2235
2240		
Phe Asp Tyr Arg Ala Gly Thr Ser Pro Gly Thr Pro Asn Arg Ile Phe		
2245	2250	2255
Phe Ser Asp Ile His Phe Gly Asn Ile Gln Gln Ile Asn Asp Asp Gly		
2260	2265	2270
Ser Arg Arg Ile Thr Ile Val Glu Asn Val Gly Ser Val Glu Gly Leu		
2275	2280	2285
Ala Tyr His Arg Gly Trp Asp Thr Leu Tyr Trp Thr Ser Tyr Thr Thr		
2290	2295	2300
Ser Thr Ile Thr Arg His Thr Val Asp Gln Thr Arg Pro Gly Ala Phe		
305	2310	2315
2320		
Glu Arg Glu Thr Val Ile Thr Met Ser Gly Asp Asp His Pro Arg Ala		
2325	2330	2335

FIG. 8b

Phe Val Leu Asp Glu Cys Gln Asn Leu Met Phe Trp Thr Asn Trp Asn
 2340 2345 2350
 Glu Gln His Pro Ser Ile Met Arg Ala Ala Leu Ser Gly Ala Asn Val
 2355 2360 2365
 Leu Thr Leu Ile Glu Lys Asp Ile Arg Thr Pro Asn Gly Leu Ala Ile
 2370 2375 2380
 Asp His Arg Ala Glu Lys Leu Tyr Phe Ser Asp Ala Thr Leu Asp Lys
 385 2390 2395 2400
 Ile Glu Arg Cys Glu Tyr Asp Gly Ser His Arg Tyr Val Ile Leu Lys
 2405 2410 2415
 Ser Glu Pro Val His Pro Phe Gly Leu Ala Val Tyr Gly Glu His Ile
 2420 2425 2430
 Phe Trp Thr Asp Trp Val Arg Arg Ala Val Gln Arg Ala Asn Lys His
 2435 2440 2445
 Val Gly Ser Asn Met Lys Leu Leu Arg Val Asp Ile Pro Gln Gln Pro
 2450 2455 2460
 Met Gly Ile Ile Ala Val Ala Asn Asp Thr Asn Ser Cys Glu Leu Ser
 465 2470 2475 2480
 Pro Cys Arg Ile Asn Asn Gly Gly Cys Gln Asp Leu Cys Leu Thr
 2485 2490 2495
 His Gln Gly His Val Asn Cys Ser Cys Arg Gly Gly Arg Ile Leu Gln
 2500 2505 2510
 Asp Asp Leu Thr Cys Arg Ala Val Asn Ser Ser Cys Arg Ala Gln Asp
 2515 2520 2525
 Glu Phe Glu Cys Ala Asn Gly Glu Cys Ile Asn Phe Ser Leu Thr Cys
 2530 2535 2540
 Asp Gly Val Pro His Cys Lys Asp Lys Ser Asp Glu Lys Pro Ser Tyr
 545 2550 2555 2560
 Cys Asn Ser Arg Arg Cys Lys Lys Thr Phe Arg Gln Cys Ser Asn Gly
 2565 2570 2575
 Arg Cys Val Ser Asn Met Leu Trp Cys Asn Gly Ala Asp Asp Cys Gly
 2580 2585 2590
 Asp Gly Ser Asp Glu Ile Pro Cys Asn Lys Thr Ala Cys Gly Val Gly
 2595 2600 2605
 Glu Phe Arg Cys Arg Asp Gly Thr Cys Ile Gly Asn Ser Ser Arg Cys
 2610 2615 2620
 Asn Gln Phe Val Asp Cys Glu Asp Ala Ser Asp Glu Met Asn Cys Ser
 625 2630 2635 2640
 Ala Thr Asp Cys Ser Ser Tyr Phe Arg Leu Gly Val Lys Gly Val Leu
 2645 2650 2655
 Phe Gln Pro Cys Glu Arg Thr Ser Leu Cys Tyr Ala Pro Ser Trp Val
 2660 2665 2670
 Cys Asp Gly Ala Asn Asp Cys Gly Asp Tyr Ser Asp Glu Arg Asp Cys
 2675 2680 2685
 Pro Gly Val Lys Arg Pro Arg Cys Pro Leu Asn Tyr Phe Ala Cys Pro
 2690 2695 2700
 Ser Gly Arg Cys Ile Pro Met Ser Trp Thr Cys Asp Lys Glu Asp Asp
 705 2710 2715 2720
 Cys Glu His Gly Glu Asp Glu Thr His Cys Asn Lys Phe Cys Ser Glu
 2725 2730 2735
 Ala Gln Phe Glu Cys Gln Asn His Arg Cys Ile Ser Lys Gln Trp Leu
 2740 2745 2750
 Cys Asp Gly Ser Asp Asp Cys Gly Asp Gly Ser Asp Glu Ala Ala His
 2755 2760 2765
 Cys Glu Gly Lys Thr Cys Gly Pro Ser Ser Phe Ser Cys Pro Gly Thr
 2770 2775 2780
 His Val Cys Val Pro Glu Arg Trp Leu Cys Asp Gly Asp Lys Asp Cys
 785 2790 2795 2800
 Ala Asp Gly Ala Asp Glu Ser Ile Ala Ala Gly Cys Leu Tyr Asn Ser

FIG. 8b

2805	2810	2815
Thr Cys Asp Asp Arg Glu Phe Met Cys Gln Asn Arg Gln Cys Ile Pro		
2820	2825	2830
Lys His Phe Val Cys Asp His Asp Arg Asp Cys Ala Asp Gly Ser Asp		
2835	2840	2845
Glu Ser Pro Glu Cys Glu Tyr Pro Thr Cys Gly Pro Ser Glu Phe Arg		
2850	2855	2860
Cys Ala Asn Gly Arg Cys Leu Ser Ser Arg Gln Trp Glu Cys Asp Gly		
865	2870	2875
Glu Asn Asp Cys His Asp Gln Ser Asp Glu Ala Pro Lys Asn Pro His		
2885	2890	2895
Cys Thr Ser Pro Glu His Lys Cys Asn Ala Ser Ser Gln Phe Leu Cys		
2900	2905	2910
Ser Ser Gly Arg Cys Val Ala Glu Ala Leu Leu Cys Asn Gly Gln Asp		
2915	2920	2925
Asp Cys Gly Asp Ser Ser Asp Glu Arg Gly Cys His Ile Asn Glu Cys		
2930	2935	2940
Leu Ser Arg Lys Leu Ser Gly Cys Ser Gln Asp Cys Glu Asp Leu Lys		
945	2950	2955
Ile Gly Phe Lys Cys Arg Cys Arg Pro Gly Phe Arg Leu Lys Asp Asp		
2965	2970	2975
Gly Arg Thr Cys Ala Asp Val Asp Glu Cys Ser Thr Thr Phe Pro Cys		
2980	2985	2990
Ser Gln Arg Cys Ile Asn Thr His Gly Ser Tyr Lys Cys Leu Cys Val		
2995	3000	3005
Glu Gly Tyr Ala Pro Arg Gly Gly Asp Pro His Ser Cys Lys Ala Val		
3010	3015	3020
Thr Asp Glu Glu Pro Phe Leu Ile Phe Ala Asn Arg Tyr Tyr Leu Arg		
025	3030	3035
Lys Leu Asn Leu Asp Gly Ser Asn Tyr Thr Leu Leu Lys Gln Gly Leu		
3045	3050	3055
Asn Asn Ala Val Ala Leu Asp Phe Asp Tyr Arg Glu Gln Met Ile Tyr		
3060	3065	3070
Trp Thr Asp Val Thr Thr Gln Gly Ser Met Ile Arg Arg Met His Leu		
3075	3080	3085
Asn Gly Ser Asn Val Gln Val Leu His Arg Thr Gly Leu Ser Asn Pro		
3090	3095	3100
Asp Gly Leu Ala Val Asp Trp Val Gly Gly Asn Leu Tyr Trp Cys Asp		
105	3110	3115
Lys Gly Arg Asp Thr Ile Glu Val Ser Lys Leu Asn Gly Ala Tyr Arg		
3125	3130	3135
Thr Val Leu Val Ser Ser Gly Leu Arg Glu Pro Arg Ala Leu Val Val		
3140	3145	3150
Asp Val Gln Asn Gly Tyr Leu Tyr Trp Thr Asp Trp Gly Asp His Ser		
3155	3160	3165
Leu Ile Gly Arg Ile Gly Met Asp Gly Ser Ser Arg Ser Val Ile Val		
3170	3175	3180
Asp Thr Lys Ile Thr Trp Pro Asn Gly Leu Thr Leu Asp Tyr Val Thr		
185	3190	3195
Glu Arg Ile Tyr Trp Ala Asp Ala Arg Glu Asp Tyr Ile Glu Phe Ala		
3205	3210	3215
Ser Leu Asp Gly Ser Asn Arg His Val Val Leu Ser Gln Asp Ile Pro		
3220	3225	3230
His Ile Phe Ala Leu Thr Leu Phe Glu Asp Tyr Val Tyr Trp Thr Asp		
3235	3240	3245
Trp Glu Thr Lys Ser Ile Asn Arg Ala His Lys Thr Thr Gly Thr Asn		
3250	3255	3260
Lys Thr Leu Leu Ile Ser Thr Leu His Arg Pro Met Asp Leu His Val		
265	3270	3275
		3280

FIG. 8b

Phe His Ala Leu Arg Gln Pro Asp Val Pro Asn His Pro Cys Lys Val
 3285 3290 3295
 Asn Asn Gly Gly Cys Ser Asn Leu Cys Leu Leu Ser Pro Gly Gly Gly
 3300 3305 3310
 His Lys Cys Ala Cys Pro Thr Asn Phe Tyr Leu Gly Ser Asp Gly Arg
 3315 3320 3325
 Thr Cys Val Ser Asn Cys Thr Ala Ser Gln Phe Val Cys Lys Asn Asp
 3330 3335 3340
 Lys Cys Ile Pro Phe Trp Trp Lys Cys Asp Thr Glu Asp Asp Cys Gly
 3345 3350 3355 3360
 Asp His Ser Asp Glu Pro Pro Asp Cys Pro Glu Phe Lys Cys Arg Pro
 3365 3370 3375
 Gly Gln Phe Gln Cys Ser Thr Gly Ile Cys Thr Asn Pro Ala Phe Ile
 3380 3385 3390
 Cys Asp Gly Asp Asn Asp Cys Gln Asp Asn Ser Asp Glu Ala Asn Cys
 3395 3400 3405
 Asp Ile His Val Cys Leu Pro Ser Gln Phe Lys Cys Thr Asn Thr Asn
 3410 3415 3420
 Arg Cys Ile Pro Gly Ile Phe Arg Cys Asn Gly Gln Asp Asn Cys Gly
 425 3430 3435 3440
 Asp Gly Glu Asp Glu Arg Asp Cys Pro Glu Val Thr Cys Ala Pro Asn
 3445 3450 3455
 Gln Phe Gln Cys Ser Ile Thr Lys Arg Cys Ile Pro Arg Val Trp Val
 3460 3465 3470
 Cys Asp Arg Asp Asn Asp Cys Val Asp Gly Ser Asp Glu Pro Ala Asn
 3475 3480 3485
 Cys Thr Gln Met Thr Cys Gly Val Asp Glu Phe Arg Cys Lys Asp Ser
 3490 3495 3500
 Gly Arg Cys Ile Pro Ala Arg Trp Lys Cys Asp Gly Glu Asp Asp Cys
 505 3510 3515 3520
 Gly Asp Gly Ser Asp Glu Pro Lys Glu Glu Cys Asp Glu Arg Thr Cys
 3525 3530 3535
 Glu Pro Tyr Gln Phe Arg Cys Lys Asn Asn Arg Cys Val Pro Gly Arg
 3540 3545 3550
 Trp Gln Cys Asp Tyr Asp Asn Asp Cys Gly Asp Asn Ser Asp Glu Glu
 3555 3560 3565
 Ser Cys Thr Pro Arg Pro Cys Ser Glu Ser Glu Phe Ser Cys Ala Asn
 3570 3575 3580
 Gly Arg Cys Ile Ala Gly Arg Trp Lys Cys Asp Gly Asp His Asp Cys
 585 3590 3595 3600
 Ala Asp Gly Ser Asp Glu Lys Asp Cys Thr Pro Arg Cys Asp Met Asp
 3605 3610 3615
 Gln Phe Gln Cys Lys Ser Gly His Cys Ile Pro Leu Arg Trp Arg Cys
 3620 3625 3630
 Asp Ala Asp Ala Asp Cys Met Asp Gly Ser Asp Glu Glu Ala Cys Gly
 3635 3640 3645
 Thr Gly Val Arg Thr Cys Pro Leu Asp Glu Phe Gln Cys Asn Asn Thr
 3650 3655 3660
 Leu Cys Lys Pro Leu Ala Trp Lys Cys Asp Gly Glu Asp Asp Cys Gly
 665 3670 3675 3680
 Asp Asn Ser Asp Glu Asn Pro Glu Glu Cys Ala Arg Phe Val Cys Pro
 3685 3690 3695
 Pro Asn Arg Pro Phe Arg Cys Lys Asn Asp Arg Val Cys Leu Trp Ile
 3700 3705 3710
 Gly Arg Gln Cys Asp Gly Thr Asp Asn Cys Gly Asp Gly Thr Asp Glu
 3715 3720 3725
 Glu Asp Cys Glu Pro Pro Thr Ala His Thr Thr His Cys Lys Asp Lys
 3730 3735 3740
 Lys Glu Phe Leu Cys Arg Asn Gln Arg Cys Leu Ser Ser Ser Leu Arg

FIG. 8b

745	3750	3755	3760												
Cys	Asn	Met	Phe	Asp	Asp	Cys	Gly	Asp	Gly	Ser	Asp	Glu	Glu	Asp	Cys
3765	3770	3775													
Ser	Ile	Asp	Pro	Lys	Leu	Thr	Ser	Cys	Ala	Thr	Asn	Ala	Ser	Ile	Cys
3780	3785	3790													
Gly	Asp	Glu	Ala	Arg	Cys	Val	Arg	Thr	Glu	Lys	Ala	Ala	Tyr	Cys	Ala
3795	3800	3805													
Cys	Arg	Ser	Gly	Phe	His	Thr	Val	Pro	Gly	Gln	Pro	Gly	Cys	Gln	Asp
3810	3815	3820													
Ile	Asn	Glu	Cys	Leu	Arg	Phe	Gly	Thr	Cys	Ser	Gln	Leu	Cys	Asn	Asn
3825	3830	3835	3840												
Thr	Lys	Gly	Gly	His	Leu	Cys	Ser	Cys	Ala	Arg	Asn	Phe	Met	Lys	Thr
3845	3850	3855													
His	Asn	Thr	Cys	Lys	Ala	Glu	Gly	Ser	Glu	Tyr	Gln	Val	Leu	Tyr	Ile
3860	3865	3870													
Ala	Asp	Asp	Asn	Glu	Ile	Arg	Ser	Leu	Phe	Pro	Gly	His	Pro	His	Ser
3875	3880	3885													
Ala	Tyr	Glu	Gln	Ala	Phe	Gln	Gly	Asp	Glu	Ser	Val	Arg	Ile	Asp	Ala
3890	3895	3900													
Met	Asp	Val	His	Val	Lys	Ala	Gly	Arg	Val	Tyr	Trp	Thr	Asn	Trp	His
3905	3910	3915	3920												
Thr	Gly	Thr	Ile	Ser	Tyr	Arg	Ser	Leu	Pro	Pro	Ala	Ala	Pro	Pro	Thr
3925	3930	3935													
Thr	Ser	Asn	Arg	His	Arg	Arg	Gin	Ile	Asp	Arg	Gly	Val	Thr	His	Leu
3940	3945	3950													
Asn	Ile	Ser	Gly	Leu	Lys	Met	Pro	Arg	Gly	Ile	Ala	Ile	Asp	Trp	Val
3955	3960	3965													
Ala	Gly	Asn	Val	Tyr	Trp	Thr	Asp	Ser	Gly	Arg	Asp	Val	Ile	Glu	Val
3970	3975	3980													
Ala	Gln	Met	Lys	Gly	Glu	Asn	Arg	Lys	Thr	Leu	Ile	Ser	Gly	Met	Ile
3985	3990	3995	4000												
Asp	Glu	Pro	His	Ala	Ile	Val	Val	Asp	Pro	Leu	Arg	Gly	Thr	Met	Tyr
4005	4010	4015													
Trp	Ser	Asp	Trp	Gly	Asn	His	Pro	Lys	Ile	Glu	Thr	Ala	Ala	Met	Asp
4020	4025	4030													
Gly	Thr	Leu	Arg	Glu	Thr	Leu	Val	Gln	Asp	Asn	Ile	Gln	Trp	Pro	Thr
4035	4040	4045													
Gly	Leu	Ala	Val	Asp	Tyr	His	Asn	Glu	Arg	Leu	Tyr	Trp	Ala	Asp	Ala
4050	4055	4060													
Lys	Leu	Ser	Val	Ile	Gly	Ser	Ile	Arg	Leu	Asn	Gly	Thr	Asp	Pro	Ile
4065	4070	4075	4080												
Val	Ala	Ala	Asp	Ser	Lys	Arg	Gly	Leu	Ser	His	Pro	Phe	Ser	Ile	Asp
4085	4090	4095													
Val	Phe	Glu	Asp	Tyr	Ile	Tyr	Gly	Val	Thr	Tyr	Ile	Asn	Arg	Val	
4100	4105	4110													
Phe	Lys	Ile	His	Lys	Phe	Gly	His	Ser	Pro	Leu	Val	Asn	Leu	Thr	Gly
4115	4120	4125													
Gly	Leu	Ser	His	Ala	Ser	Asp	Val	Val	Leu	Tyr	His	Gln	His	Lys	Gln
4130	4135	4140													
Pro	Glu	Val	Thr	Asn	Pro	Cys	Asp	Arg	Lys	Lys	Cys	Glu	Trp	Leu	Cys
4145	4150	4155	4160												
Leu	Leu	Ser	Pro	Ser	Gly	Pro	Val	Cys	Thr	Cys	Pro	Asn	Gly	Lys	Arg
4165	4170	4175													
Leu	Asp	Asn	Gly	Thr	Cys	Val	Pro	Val	Pro	Ser	Pro	Thr	Pro	Pro	Pro
4180	4185	4190													
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4195	4200	4205													
Ser	Cys	Phe	Leu	Asn	Ala	Arg	Arg	Gln	Pro	Lys	Cys	Arg	Cys	Gln	Pro
4210	4215	4220													

FIG. 8b

Arg Tyr Thr Gly Asp Lys Cys Glu Leu Asp Gln Cys Trp Glu His Cys
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 Arg Asn Gly Gly Thr Cys Ala Ala Ser Pro Ser Gly Met Pro Thr Cys
 4245 4250 4255
 Arg Cys Pro Thr Gly Phe Thr Gly Pro Lys Cys Thr Gln Gln Val Cys
 4260 4265 4270
 Ala Gly Tyr Cys Ala Asn Asn Ser Thr Cys Thr Val Asn Gln Gly Asn
 4275 4280 4285
 Gln Pro Gln Cys Arg Cys Leu Pro Gly Phe Leu Gly Asp Arg Cys Gln
 4290 4295 4300
 Tyr Arg Gln Cys Ser Gly Tyr Cys Glu Asn Phe Gly Thr Cys Gln Met
 305 4310 4315 4320
 Ala Ala Asp Gly Ser Arg Gln Cys Arg Cys Thr Ala Tyr Phe Glu Gly
 4325 4330 4335
 Ser Arg Cys Glu Val Asn Lys Cys Ser Arg Cys Leu Glu Gly Ala Cys
 4340 4345 4350
 Val Val Asn Lys Gln Ser Gly Asp Val Thr Cys Asn Cys Thr Asp Gly
 4355 4360 4365
 Arg Val Ala Pro Ser Cys Leu Thr Cys Val Gly His Cys Ser Asn Gly
 4370 4375 4380
 Gly Ser Cys Thr Met Asn Ser Lys Met Met Pro Glu Cys Gln Cys Pro
 385 4390 4395 4400
 Pro His Met Thr Gly Pro Arg Cys Glu Glu His Val Phe Ser Gln Gln
 4405 4410 4415
 Gln Pro Gly His Ile Ala Ser Ile Leu Ile Pro Leu Leu Leu Leu
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 4435 4440 4445
 Gln Gly Ala Lys Gly Phe Gln His Gln Arg Met Thr Asn Gly Ala Met
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 Asn Val Glu Ile Gly Asn Pro Thr Tyr Lys Met Tyr Glu Gly Glu
 4465 4470 4475 4480
 Pro Asp Asp Val Gly Gly Leu Leu Asp Ala Asp Phe Ala Leu Asp Pro
 4485 4490 4495
 Asp Lys Pro Thr Asn Phe Thr Asn Pro Val Tyr Ala Thr Leu Tyr Met
 4500 4505 4510
 Gly Gly His Gly Ser Arg His Ser Leu Ala Ser Thr Asp Glu Lys Arg
 4515 4520 4525
 Glu Leu Leu Gly Arg Gly Pro Glu Asp Glu Ile Gly Asp Pro Leu Ala
 4530 4535 4540

FIG. 8b

**DECLARATION
AND POWER OF ATTORNEY**

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below at 201 et seq. underneath my name.

I believe I am the original, first and sole inventor if only one name is listed at 201 below, or an original, first and joint inventor if plural names are listed at 201 et seq. below, of the subject matter which is claimed and for which a patent is sought on the invention entitled

ALPHA (2) MACROGLOBULIN RECEPTOR AS A HEAT SHOCK PROTEIN RECEPTOR AND USES THEREOF

and for which a patent application:

is attached hereto and includes amendment(s) filed on *(if applicable)*
 was filed in the United States on as Application No. *(for declaration not accompanying application)*
 with amendment(s) filed on *(if applicable)*
 was filed as PCT international Application No. on and was amended under PCT Article 19 on *(if applicable)*

I hereby state that I have reviewed and understand the contents of the above identified application, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

EARLIEST FOREIGN APPLICATION(S), IF ANY, FILED PRIOR TO THE FILING DATE OF THE APPLICATION			
APPLICATION NUMBER	COUNTRY	DATE OF FILING (day, month, year)	PRIORITY CLAIMED
			YES <input type="checkbox"/> NO <input type="checkbox"/>
			YES <input type="checkbox"/> NO <input type="checkbox"/>

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

APPLICATION NUMBER	FILING DATE
60/209,095	June 2, 2000

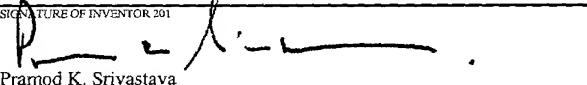
I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NO.	FILING DATE	STATUS		
		PATENTED	PENDING	ABANDONED

POWER OF ATTORNEY: As a named inventor, I hereby appoint S. Leslie Misrock (Reg. No. 18872), Harry C. Jones, III (Reg. No. 20280), Berj A. Terzian (Reg. No. 20060), David Weild, III (Reg. No. 21094), Jonathan A. Marshall (Reg. No. 24614), Barry D. Rein (Reg. No. 22411), Stanton T. Lawrence, III (Reg. No. 25736), Charles E. McKenney (Reg. No. 22795), Philip T. Shannon (Reg. No. 24278), Francis E. Morris (Reg. No. 24615), Charles E. Miller (Reg. No. 24576), Gidon D. Stern (Reg. No. 27469), John J. Lauter, Jr. (Reg. No. 27814), Brian M. Poissant (Reg. No. 28462), Brian D. Coggio (Reg. No. 27624), Rory J. Radding (Reg. No. 28749), Stephen J. Harbulak (Reg. No. 29166), Donald J. Goodell (Reg. No. 19766), James N. Paik (Reg. No. 25510), Thomas E. Friebel (Reg. No. 29258), Laura A. Coruzzi (Reg. No. 30742), Jeninifer Gordon (Reg. No. 30753), Allan A. Fanucci (Reg. No. 30256), Geraldine F. Baldwin (Reg. No. 31232), Victor N. Balancia (Reg. No. 31231), Samuel B. Abrams (Reg. No. 30605), Steven I. Wallach (Reg. No. 35402), Marcia H. Sundeen (Reg. No. 30893), Paul J. Zegger (Reg. No. 33821), Edmond R. Bannon (Reg. No. 32110), Bruce J. Barker (Reg. No. 33291), Adriane M. Antler (Reg. No. 32605), Thomas G. Rowan (Reg. No. 34419), James G. Markey (Reg. No. 31636), Thomas D. Kohler (Reg. No. 32797), Scott D. Stimpson (Reg. No. 33607), Gary S. Williams (Reg. No. 31066), Wilham S. Galliani (Reg. No. 33885), Ann L. Gisolfi (Reg. No. 31956), Todd A. Wagner (Reg. No. 35399), Scott B. Familiant (Reg. No. 35514), Kelly D. Talcott (Reg. No. 39582), Francis D. Cerrito (Reg. No. 38100), Anthony M. Insogna (Reg. No. 35203), Brian M. Rothery (Reg. No. 35340), Brian D. Siff (Reg. No. 35679), and Alan Tenenbaum (Reg. No. 34939), all of Pennie & Edmonds LLP, whose addresses are 1155 Avenue of the Americas, New York, New York 10036, 1667 K Street N.W., Washington, DC 20006 and 3300 Hillview Avenue, Palo Alto, CA 94304, and each of them, my attorneys, to prosecute this application, and to transact all business in the Patent and Trademark Office connected therewith.

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	RESIDENCE & CITIZENSHIP	CITY Avon	STATE OR FOREIGN COUNTRY Connecticut	COUNTRY OF CITIZENSHIP India		
	POST OFFICE ADDRESS	STREET 70 Pheasant Run	CITY Avon	STATE OR COUNTRY Connecticut	ZIP CODE 06001	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201	
Pramod K. Srivastava	
DATE	7-24-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Pramod K. Srivastava

Application No.: To be assigned

Group Art Unit: To be assigned

Filed: Concurrently herewith

Examiner: To be assigned

For: ALPHA (2) MACROGLOBULIN
RECEPTOR AS A HEAT SHOCK
PROTEIN RECEPTOR AND USES
THEREOF

Attorney Docket No.: 8449-123

TRANSMITTAL OF SEQUENCE LISTING UNDER 37 C.F.R. § 1.821

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In accordance with 37 C.F.R. § 1.821, Applicant submits herewith a Sequence Listing in paper and computer-readable form pursuant to 37 C.F.R. §§ 1.821(c) and (e).

I hereby state that the content of the paper and computer-readable copies of the Sequence Listing, submitted in accordance with 37 C.F.R. §§ 1.821(c) and (e), respectively, are the same.

Respectfully submitted,

Date: July 25, 2000

Adriane M. Antler

32,605

Adriane M. Antler

(Reg. No.)

PENNIE & EDMONDS LLP by *Eileen E. Falvey*
1155 Avenue of the Americas
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(212) 790-9090

Reg No. 46097

Enclosure

SEQUENCE LISTING

<110> Pramod K. Srivastava

<120> ALPHA(2) MACROGLOBULIN RECEPTOR AS A HEAT SHOCK PROTEIN RECEPTOR AND USES THEREOF

<130> 8449-123

<150> 60/209,095

<151> 2000-06-02

<160> 57

<170> FastSEQ for Windows Version 3.0

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aaggaggtgg	gcccacacca	ggaagggaaa	gcgggcagcc	ccgttttggg	gacgtgaacg	14820
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attgtaaaaa	aaaaaaa					14896

<210> 7
 <211> 126
 <212> PRT
 <213> Homo sapiens

<400> 7
 Ile Ala Leu Asp Phe His Leu Ser Gln Ser Ala Leu Tyr Trp Thr Asp
 1 5 10 15
 Val Val Glu Asp Lys Ile Tyr Arg Gly Lys Leu Leu Asp Asn Gly Ala
 20 25 30
 Leu Thr Ser Phe Glu Val Val Ile Gln Tyr Gly Leu Ala Thr Pro Glu
 35 40 45
 Gly Leu Ala Val Asp Trp Ile Ala Gly Asn Ile Tyr Trp Val Glu Ser
 50 55 60
 Asn Leu Asp Gln Ile Glu Val Ala Lys Leu Asp Gly Thr Leu Arg Thr
 65 70 75 80
 Thr Leu Leu Ala Gly Asp Ile Glu His Pro Arg Ala Ile Ala Leu Asp
 85 90 95
 Pro Arg Asp Gly Ile Leu Phe Trp Thr Asp Trp Asp Ala Ser Leu Pro
 100 105 110
 Arg Ile Glu Ala Ala Ser Met Ser Gly Ala Gly Arg Arg Thr
 115 120 125

<210> 8
 <211> 153
 <212> PRT
 <213> Homo sapiens

<400> 8
 Leu Leu Gln Gln Val Ser Leu Pro Glu Leu Pro Gly Glu Tyr Ser Met
 1 5 10 15
 Lys Val Thr Gly Glu Gly Cys Val Tyr Leu Gln Thr Ser Leu Lys Tyr
 20 25 30
 Asn Ile Leu Pro Glu Lys Glu Glu Phe Pro Phe Ala Leu Gly Val Gln
 35 40 45
 Thr Leu Pro Gln Thr Cys Asp Glu Pro Lys Ala His Thr Ser Phe Gln
 50 55 60
 Ile Ser Leu Ser Val Ser Tyr Thr Gly Ser Arg Ser Ala Ser Asn Met
 65 70 75 80
 Ala Ile Val Asp Val Lys Met Val Ser Gly Phe Ile Pro Leu Lys Pro
 85 90 95

Thr Val Lys Met Leu Glu Arg Ser Asn His Val Ser Arg Thr Glu Val
 100 105 110
 Ser Ser Asn His Val Leu Ile Tyr Leu Asp Lys Val Ser Asn Gln Thr
 115 120 125
 Leu Ser Leu Phe Phe Thr Val Leu Gln Asp Val Pro Val Arg Asp Leu
 130 135 140
 Lys Pro Ala Ile Val Lys Val Tyr Asp
 145 150

<210> 9
 <211> 138
 <212> PRT
 <213> Homo sapiens

<400> 9
 Met Lys Val Thr Gly Glu Gly Cys Val Tyr Leu Gln Thr Ser Leu Lys
 1 5 10 15
 Tyr Asn Ile Leu Pro Glu Lys Glu Glu Phe Pro Phe Ala Leu Gly Val
 20 25 30
 Gln Thr Leu Pro Gln Thr Cys Asp Glu Pro Lys Ala His Thr Ser Phe
 35 40 45
 Gln Ile Ser Leu Ser Val Ser Tyr Thr Gly Ser Arg Ser Ala Ser Asn
 50 55 60
 Met Ala Ile Val Asp Val Lys Met Val Ser Gly Phe Ile Pro Leu Lys
 65 70 75 80
 Pro Thr Val Lys Met Leu Glu Arg Ser Asn His Val Ser Arg Thr Glu
 85 90 95
 Val Ser Ser Asn His Val Leu Ile Tyr Leu Asp Lys Val Ser Asn Gln
 100 105 110
 Thr Leu Ser Leu Phe Phe Thr Val Leu Gln Asp Val Pro Val Arg Asp
 115 120 125
 Leu Lys Pro Ala Ile Val Lys Val Tyr Asp
 130 135

<210> 10
 <211> 27
 <212> PRT
 <213> Homo sapiens

<400> 10
 Ser Val Ser Tyr Thr Gly Ser Arg Ser Ala Ser Asn Met Ala Ile Val
 1 5 10 15
 Asp Val Lys Met Val Ser Gly Phe Ile Pro Leu
 20 25

<210> 11
 <211> 126
 <212> PRT
 <213> Homo sapiens

<400> 11
 Leu Gln Gln Val Ser Leu Pro Glu Leu Pro Gly Glu Tyr Ser Met Lys
 1 5 10 15
 Val Thr Gly Glu Gly Cys Val Tyr Leu Gln Thr Ser Leu Lys Tyr Asn
 20 25 30
 Ile Leu Pro Glu Lys Glu Glu Phe Pro Phe Ala Leu Gly Val Gln Thr
 35 40 45

Leu Pro Gln Thr Cys Asp Glu Pro Lys Ala His Thr Ser Phe Gln Ile
50 55 60
Ser Leu Ser Val Ser Tyr Thr Gly Ser Arg Ser Ala Ser Asn Met Ala
65 70 75 80
Ile Val Asp Val Lys Met Val Ser Gly Phe Ile Pro Leu Lys Pro Thr
85 90 95
Val Lys Met Leu Glu Arg Ser Asn His Val Ser Arg Thr Glu Val Ser
100 105 110
Ser Asn His Val Leu Ile Tyr Leu Asp Lys Val Ser Asn Gln
115 120 125

<210> 12
<211> 111
<212> PRT
<213> Homo sapiens

<400> 12
Leu Gln Gln Val Ser Leu Pro Glu Leu Pro Gly Glu Tyr Ser Met Lys
1 5 10 15
Val Thr Gly Glu Gly Cys Val Tyr Leu Gln Thr Ser Leu Lys Tyr Asn
20 25 30
Ile Leu Pro Glu Lys Glu Glu Phe Pro Phe Ala Leu Gly Val Gln Thr
35 40 45
Leu Pro Gln Thr Cys Asp Glu Pro Lys Ala His Thr Ser Phe Gln Ile
50 55 60
Ser Leu Ser Val Ser Tyr Thr Gly Ser Arg Ser Ala Ser Asn Met Ala
65 70 75 80
Ile Val Asp Val Lys Met Val Ser Gly Phe Ile Pro Leu Lys Pro Thr
85 90 95
Val Lys Met Leu Glu Arg Ser Asn His Val Ser Arg Thr Glu Val
100 105 110

<210> 13
<211> 81
<212> PRT
<213> Homo sapiens

<400> 13
Leu Gln Gln Val Ser Leu Pro Glu Leu Pro Gly Glu Tyr Ser Met Lys
1 5 10 15
Val Thr Gly Glu Gly Cys Val Tyr Leu Gln Thr Ser Leu Lys Tyr Asn
20 25 30
Ile Leu Pro Glu Lys Glu Glu Phe Pro Phe Ala Leu Gly Val Gln Thr
35 40 45
Leu Pro Gln Thr Cys Asp Glu Pro Lys Ala His Thr Ser Phe Gln Ile
50 55 60
Ser Leu Ser Val Ser Tyr Thr Gly Ser Arg Ser Ala Ser Asn Met Ala
65 70 75 80
Ile

<210> 14
<211> 101
<212> PRT
<213> Homo sapiens

<400> 14

Gln Thr Ser Leu Lys Tyr Asn Ile Leu Pro Glu Lys Glu Glu Phe Pro
1 5 10 15
Phe Ala Leu Gly Val Gln Thr Leu Pro Gln Thr Cys Asp Glu Pro Lys
20 25 30
Ala His Thr Ser Phe Gln Ile Ser Leu Ser Val Ser Tyr Thr Gly Ser
35 40 45
Arg Ser Ala Ser Asn Met Ala Ile Val Asp Val Lys Met Val Ser Gly
50 55 60
Phe Ile Pro Leu Lys Pro Thr Val Lys Met Leu Glu Arg Ser Asn His
65 70 75 80
Val Ser Arg Thr Glu Val Ser Ser Asn His Val Leu Ile Tyr Leu Asp
85 90 95
Lys Val Ser Asn Gln
100

<210> 15
<211> 76
<212> PRT
<213> Homo sapiens

<400> 15

Gln Thr Ser Leu Lys Tyr Asn Ile Leu Pro Glu Lys Glu Glu Phe Pro
1 5 10 15
Phe Ala Leu Gly Val Gln Thr Leu Pro Gln Thr Cys Asp Glu Pro Lys
20 25 30
Ala His Thr Ser Phe Gln Ile Ser Leu Ser Val Ser Tyr Thr Gly Ser
35 40 45
Arg Ser Ala Ser Asn Met Ala Ile Val Asp Val Lys Met Val Ser Gly
50 55 60
Phe Ile Pro Leu Lys Pro Thr Val Lys Met Leu Glu
65 70 75

<210> 16
<211> 56
<212> PRT
<213> Homo sapiens

<400> 16

Gln Thr Ser Leu Lys Tyr Asn Ile Leu Pro Glu Lys Glu Glu Phe Pro
1 5 10 15
Phe Ala Leu Gly Val Gln Thr Leu Pro Gln Thr Cys Asp Glu Pro Lys
20 25 30
Ala His Thr Ser Phe Gln Ile Ser Leu Ser Val Ser Tyr Thr Gly Ser
35 40 45
Arg Ser Ala Ser Asn Met Ala Ile
50 55

<210> 17
<211> 76
<212> PRT
<213> Homo sapiens

<400> 17

Gln Thr Cys Asp Glu Pro Lys Ala His Thr Ser Phe Gln Ile Ser Leu
1 5 10 15
Ser Val Ser Tyr Thr Gly Ser Arg Ser Ala Ser Asn Met Ala Ile Val
20 25 30

Asp Val Lys Met Val Ser Gly Phe Ile Pro Leu Lys Pro Thr Val Lys
 35 40 45
 Met Leu Glu Arg Ser Asn His Val Ser Arg Thr Glu Val Ser Ser Asn
 50 55 60
 His Val Leu Ile Tyr Leu Asp Lys Val Ser Asn Gln
 65 70 75

<210> 18
 <211> 76
 <212> PRT
 <213> Homo sapiens

<400> 18
 Gln Thr Cys Asp Glu Pro Lys Ala His Thr Ser Phe Gln Ile Ser Leu
 1 5 10 15
 Ser Val Ser Tyr Thr Gly Ser Arg Ser Ala Ser Asn Met Ala Ile Val
 20 25 30
 Asp Val Lys Met Val Ser Gly Phe Ile Pro Leu Lys Pro Thr Val Lys
 35 40 45
 Met Leu Glu Arg Ser Asn His Val Ser Arg Thr Glu Val Ser Ser Asn
 50 55 60
 His Val Leu Ile Tyr Leu Asp Lys Val Ser Asn Gln
 65 70 75

<210> 19
 <211> 31
 <212> PRT
 <213> Homo sapiens

<400> 19
 Gln Thr Cys Asp Glu Pro Lys Ala His Thr Ser Phe Gln Ile Ser Leu
 1 5 10 15
 Ser Val Ser Tyr Thr Gly Ser Arg Ser Ala Ser Asn Met Ala Ile
 20 25 30

<210> 20
 <211> 44
 <212> PRT
 <213> Homo sapiens

<400> 20
 Lys Thr Cys Ser Pro Lys Gln Phe Ala Cys Arg Asp Gln Ile Thr Cys
 1 5 10 15
 Ile Ser Lys Gly Trp Arg Cys Asp Gly Glu Arg Asp Cys Pro Asp Gly
 20 25 30
 Ser Asp Glu Ala Pro Glu Ile Cys Pro Gln Ser Lys
 35 40

<210> 21
 <211> 86
 <212> PRT
 <213> Homo sapiens

<400> 21
 Lys Thr Cys Ser Pro Lys Gln Phe Ala Cys Arg Asp Gln Ile Thr Cys
 1 5 10 15
 Ile Ser Lys Gly Trp Arg Cys Asp Gly Glu Arg Asp Cys Pro Asp Gly
 20 25 30

Ser Asp Glu Ala Pro Glu Ile Cys Pro Gln Ser Lys Ala Gln Arg Cys
 35 40 45
 Gln Pro Asn Glu His Asn Cys Leu Gly Thr Glu Leu Cys Val Pro Met
 50 55 60
 Ser Arg Leu Cys Asn Gly Val Gln Asp Cys Met Asp Gly Ser Asp Glu
 65 70 75 80
 Gly Pro His Cys Arg Glu
 85

<210> 22
 <211> 43
 <212> PRT
 <213> Homo sapiens

<400> 22
 Lys Ala Gln Arg Cys Gln Pro Asn Glu His Asn Cys Leu Gly Thr Glu
 1 5 10 15
 Leu Cys Val Pro Met Ser Arg Leu Cys Asn Gly Val Gln Asp Cys Met
 20 25 30
 Asp Gly Ser Asp Glu Gly Pro His Cys Arg Glu
 35 40

<210> 23
 <211> 42
 <212> PRT
 <213> Homo sapiens

<400> 23
 Gln Cys Gln Pro Gly Glu Phe Ala Cys Ala Asn Ser Arg Cys Ile Gln
 1 5 10 15
 Glu Arg Trp Lys Cys Asp Gly Asp Asn Asp Cys Leu Asp Asn Ser Asp
 20 25 30
 Glu Ala Pro Ala Leu Cys His Gln His Thr
 35 40

<210> 24
 <211> 82
 <212> PRT
 <213> Homo sapiens

<400> 24
 Gln Cys Gln Pro Gly Glu Phe Ala Cys Ala Asn Ser Arg Cys Ile Gln
 1 5 10 15
 Glu Arg Trp Lys Cys Asp Gly Asp Asn Asp Cys Leu Asp Asn Ser Asp
 20 25 30
 Glu Ala Pro Ala Leu Cys His Gln His Thr Cys Pro Ser Asp Arg Phe
 35 40 45
 Lys Cys Glu Asn Asn Arg Cys Ile Pro Asn Arg Trp Leu Cys Asp Gly
 50 55 60
 Asp Asn Asp Cys Gly Asn Ser Glu Asp Glu Ser Asn Ala Thr Cys Ser
 65 70 75 80
 Ala Arg

<210> 25
 <211> 122
 <212> PRT
 <213> Homo sapiens

<400> 25

Gln Cys Gln Pro Gly Glu Phe Ala Cys Ala Asn Ser Arg Cys Ile Gln
1 5 10 15
Glu Arg Trp Lys Cys Asp Gly Asp Asn Asp Cys Leu Asp Asn Ser Asp
20 25 30
Glu Ala Pro Ala Leu Cys His Gln His Thr Cys Pro Ser Asp Arg Phe
35 40 45
Lys Cys Glu Asn Asn Arg Cys Ile Pro Asn Arg Trp Leu Cys Asp Gly
50 55 60
Asp Asn Asp Cys Gly Asn Ser Glu Asp Glu Ser Asn Ala Thr Cys Ser
65 70 75 80
Ala Arg Thr Cys Pro Pro Asn Gln Phe Ser Cys Ala Ser Gly Arg Cys
85 90 95
Ile Pro Ile Ser Trp Thr Cys Asp Leu Asp Asp Asp Cys Gly Asp Arg
100 105 110
Ser Asp Glu Ser Ala Ser Cys Ala Tyr Pro
115 120

<210> 26

<211> 161

<212> PRT

<213> Homo sapiens

<400> 26

Gln Cys Gln Pro Gly Glu Phe Ala Cys Ala Asn Ser Arg Cys Ile Gln
1 5 10 15
Glu Arg Trp Lys Cys Asp Gly Asp Asn Asp Cys Leu Asp Asn Ser Asp
20 25 30
Glu Ala Pro Ala Leu Cys His Gln His Thr Cys Pro Ser Asp Arg Phe
35 40 45
Lys Cys Glu Asn Asn Arg Cys Ile Pro Asn Arg Trp Leu Cys Asp Gly
50 55 60
Asp Asn Asp Cys Gly Asn Ser Glu Asp Glu Ser Asn Ala Thr Cys Ser
65 70 75 80
Ala Arg Thr Cys Pro Pro Asn Gln Phe Ser Cys Ala Ser Gly Arg Cys
85 90 95
Ile Pro Ile Ser Trp Thr Cys Asp Leu Asp Asp Asp Cys Gly Asp Arg
100 105 110
Ser Asp Glu Ser Ala Ser Cys Ala Tyr Pro Thr Cys Phe Pro Leu Thr
115 120 125
Gln Phe Thr Cys Asn Asn Gly Arg Cys Ile Asn Ile Asn Trp Arg Cys
130 135 140
Asp Asn Asp Asn Asp Cys Gly Asp Asn Ser Asp Glu Ala Gly Cys Ser
145 150 155 160
His

<210> 27

<211> 208

<212> PRT

<213> Homo sapiens

<400> 27

Gln Cys Gln Pro Gly Glu Phe Ala Cys Ala Asn Ser Arg Cys Ile Gln
1 5 10 15
Glu Arg Trp Lys Cys Asp Gly Asp Asn Asp Cys Leu Asp Asn Ser Asp
20 25 30

Glu Ala Pro Ala Leu Cys His Gln His Thr Cys Pro Ser Asp Arg Phe
 35 40 45
 Lys Cys Glu Asn Asn Arg Cys Ile Pro Asn Arg Trp Leu Cys Asp Gly
 50 55 60
 Asp Asn Asp Cys Gly Asn Ser Glu Asp Glu Ser Asn Ala Thr Cys Ser
 65 70 75 80
 Ala Arg Thr Cys Pro Pro Asn Gln Phe Ser Cys Ala Ser Gly Arg Cys
 85 90 95
 Ile Pro Ile Ser Trp Thr Cys Asp Leu Asp Asp Asp Cys Gly Asp Arg
 100 105 110
 Ser Asp Glu Ser Ala Ser Cys Ala Tyr Pro Thr Cys Phe Pro Leu Thr
 115 120 125
 Gln Phe Thr Cys Asn Asn Gly Arg Cys Ile Asn Ile Asn Trp Arg Cys
 130 135 140
 Asp Asn Asp Asn Asp Cys Gly Asp Asn Ser Asp Glu Ala Gly Cys Ser
 145 150 155 160
 His Ser Cys Ser Ser Thr Gln Phe Lys Cys Asn Ser Gly Arg Cys Ile
 165 170 175
 Pro Glu His Trp Thr Cys Asp Gly Asp Asn Asp Cys Gly Asp Tyr Ser
 180 185 190
 Asp Glu Thr His Ala Asn Cys Thr Asn Gln Ala Thr Arg Pro Pro Gly
 195 200 205

<210> 28
 <211> 150
 <212> PRT
 <213> Homo sapiens

<400> 28
 Gln Cys Gln Pro Gly Glu Ala Cys Ala Asn Ser Arg Cys Ile Gln
 1 5 10 15
 Glu Arg Trp Lys Cys Asp Gly Asp Asn Asp Cys Leu Asp Asn Ser Asp
 20 25 30
 Glu Ala Pro Ala Leu Cys His Gln His Thr Cys Pro Ser Asp Arg Phe
 35 40 45
 Lys Cys Glu Asn Asn Arg Cys Ile Pro Asn Arg Trp Leu Cys Asp Gly
 50 55 60
 Asp Asn Asp Cys Gly Asn Ser Glu Asp Glu Ser Asn Ala Thr Cys Ser
 65 70 75 80
 Ala Arg Thr Cys Pro Pro Asn Gln Phe Ser Cys Ala Ser Gly Arg Cys
 85 90 95
 Ile Pro Ile Ser Trp Thr Cys Asp Leu Asp Asp Asp Cys Gly Asp Arg
 100 105 110
 Ser Asp Glu Ser Ala Ser Cys Ala Tyr Pro Thr Cys Phe Pro Leu Thr
 115 120 125
 Gln Phe Thr Cys Asn Asn Gly Arg Cys Ile Asn Ile Asn Trp Arg Cys
 130 135 140
 Asp Asn Asp Asn Asp Cys
 145 150

<210> 29
 <211> 231
 <212> PRT
 <213> Homo sapiens

<400> 29
 Gln Cys Gln Pro Gly Glu Ala Cys Ala Asn Ser Arg Cys Ile Gln
 1 5 10 15

Glu Arg Trp Lys Cys Asp Gly Asp Asn Asp Cys Leu Asp Asn Ser Asp
 20 25 30
 Glu Ala Pro Ala Leu Cys His Gln His Thr Cys Pro Ser Asp Arg Phe
 35 40 45
 Lys Cys Glu Asn Asn Arg Cys Ile Pro Asn Arg Trp Leu Cys Asp Gly
 50 55 60
 Asp Asn Asp Cys Gly Asn Ser Glu Asp Glu Ser Asn Ala Thr Cys Ser
 65 70 75 80
 Ala Arg Thr Cys Pro Pro Asn Gln Phe Ser Cys Ala Ser Gly Arg Cys
 85 90 95
 Ile Pro Ile Ser Trp Thr Cys Asp Leu Asp Asp Asp Cys Gly Asp Arg
 100 105 110
 Ser Asp Glu Ser Ala Ser Cys Ala Tyr Pro Thr Cys Phe Pro Leu Thr
 115 120 125
 Gln Phe Thr Cys Asn Asn Gly Arg Cys Ile Asn Ile Asn Trp Arg Cys
 130 135 140
 Asp Asn Asp Asn Asp Cys Gly Asp Asn Ser Asp Glu Ala Gly Cys Ser
 145 150 155 160
 His Ser Cys Ser Ser Thr Gln Phe Lys Cys Asn Ser Gly Arg Cys Ile
 165 170 175
 Pro Glu His Trp Thr Cys Asp Gly Asp Asn Asp Cys Gly Asp Tyr Ser
 180 185 190
 Asp Glu Thr His Ala Asn Cys Thr Asn Gln Ala Thr Arg Pro Pro Gly
 195 200 205
 Gly Cys His Thr Asp Glu Phe Gln Cys Arg Leu Asp Gly Leu Cys Ile
 210 215 220
 Pro Leu Arg Trp Arg Cys Asp
 225 230

<210> 30
 <211> 40
 <212> PRT
 <213> Homo sapiens

<400> 30
 Cys Pro Ser Asp Arg Phe Lys Cys Glu Asn Asn Arg Cys Ile Pro Asn
 1 5 10 15
 Arg Trp Leu Cys Asp Gly Asp Asn Asp Cys Gly Asn Ser Glu Asp Glu
 20 25 30
 Ser Asn Ala Thr Cys Ser Ala Arg
 35 40

<210> 31
 <211> 80
 <212> PRT
 <213> Homo sapiens

<400> 31
 Cys Pro Ser Asp Arg Phe Lys Cys Glu Asn Asn Arg Cys Ile Pro Asn
 1 5 10 15
 Arg Trp Leu Cys Asp Gly Asp Asn Asp Cys Gly Asn Ser Glu Asp Glu
 20 25 30
 Ser Asn Ala Thr Cys Ser Ala Arg Thr Cys Pro Pro Asn Gln Phe Ser
 35 40 45
 Cys Ala Ser Gly Arg Cys Ile Pro Ile Ser Trp Thr Cys Asp Leu Asp
 50 55 60
 Asp Asp Cys Gly Asp Arg Ser Asp Glu Ser Ala Ser Cys Ala Tyr Pro
 65 70 75 80

<210> 32
<211> 119
<212> PRT
<213> Homo sapiens

<400> 32
Cys Pro Ser Asp Arg Phe Lys Cys Glu Asn Asn Arg Cys Ile Pro Asn
1 5 10 15
Arg Trp Leu Cys Asp Gly Asp Asn Asp Cys Gly Asn Ser Glu Asp Glu
20 25 30
Ser Asn Ala Thr Cys Ser Ala Arg Thr Cys Pro Pro Asn Gln Phe Ser
35 40 45
Cys Ala Ser Gly Arg Cys Ile Pro Ile Ser Trp Thr Cys Asp Leu Asp
50 55 60
Asp Asp Cys Gly Asp Arg Ser Asp Glu Ser Ala Ser Cys Ala Tyr Pro
65 70 75 80
Thr Cys Phe Pro Leu Thr Gln Phe Thr Cys Asn Asn Gly Arg Cys Ile
85 90 95
Asn Ile Asn Trp Arg Cys Asp Asn Asp Cys Gly Asp Asn Ser
100 105 110
Asp Glu Ala Gly Cys Ser His
115

<210> 33
<211> 166
<212> PRT
<213> Homo sapiens

<400> 33
Cys Pro Ser Asp Arg Phe Lys Cys Glu Asn Asn Arg Cys Ile Pro Asn
1 5 10 15
Arg Trp Leu Cys Asp Gly Asp Asn Asp Cys Gly Asn Ser Glu Asp Glu
20 25 30
Ser Asn Ala Thr Cys Ser Ala Arg Thr Cys Pro Pro Asn Gln Phe Ser
35 40 45
Cys Ala Ser Gly Arg Cys Ile Pro Ile Ser Trp Thr Cys Asp Leu Asp
50 55 60
Asp Asp Cys Gly Asp Arg Ser Asp Glu Ser Ala Ser Cys Ala Tyr Pro
65 70 75 80
Thr Cys Phe Pro Leu Thr Gln Phe Thr Cys Asn Asn Gly Arg Cys Ile
85 90 95
Asn Ile Asn Trp Arg Cys Asp Asn Asp Cys Gly Asp Asn Ser
100 105 110
Asp Glu Ala Gly Cys Ser His Ser Cys Ser Ser Thr Gln Phe Lys Cys
115 120 125
Asn Ser Gly Arg Cys Ile Pro Glu His Trp Thr Cys Asp Gly Asp Asn
130 135 140
Asp Cys Gly Asp Tyr Ser Asp Glu Thr His Ala Asn Cys Thr Asn Gln
145 150 155 160
Ala Thr Arg Pro Pro Gly
165

<210> 34
<211> 108
<212> PRT
<213> Homo sapiens

<400> 34

Cys Pro Ser Asp Arg Phe Lys Cys Glu Asn Asn Arg Cys Ile Pro Asn
 1 5 10 15
 Arg Trp Leu Cys Asp Gly Asp Asn Asp Cys Gly Asn Ser Glu Asp Glu
 20 25 30
 Ser Asn Ala Thr Cys Ser Ala Arg Thr Cys Pro Pro Asn Gln Phe Ser
 35 40 45
 Cys Ala Ser Gly Arg Cys Ile Pro Ile Ser Trp Thr Cys Asp Leu Asp
 50 55 60
 Asp Asp Cys Gly Asp Arg Ser Asp Glu Ser Ala Ser Cys Ala Tyr Pro
 65 70 75 80
 Thr Cys Phe Pro Leu Thr Gln Phe Thr Cys Asn Asn Gly Arg Cys Ile
 85 90 95
 Asn Ile Asn Trp Arg Cys Asp Asn Asp Asn Asp Cys
 100 105

<210> 35
 <211> 289
 <212> PRT
 <213> Homo sapiens

<400> 35

Cys Pro Ser Asp Arg Phe Lys Cys Glu Asn Asn Arg Cys Ile Pro Asn
 1 5 10 15
 Arg Trp Leu Cys Asp Gly Asp Asn Asp Cys Gly Asn Ser Glu Asp Glu
 20 25 30
 Ser Asn Ala Thr Cys Ser Ala Arg Thr Cys Pro Pro Asn Gln Phe Ser
 35 40 45
 Cys Ala Ser Gly Arg Cys Ile Pro Ile Ser Trp Thr Cys Asp Leu Asp
 50 55 60
 Asp Asp Cys Gly Asp Arg Ser Asp Glu Ser Ala Ser Cys Ala Tyr Pro
 65 70 75 80
 Thr Cys Phe Pro Leu Thr Gln Phe Thr Cys Asn Asn Gly Arg Cys Ile
 85 90 95
 Asn Ile Asn Trp Arg Cys Asp Asn Asp Asn Asp Cys Gly Asp Asn Ser
 100 105 110
 Asp Glu Ala Gly Cys Ser His Ser Cys Ser Ser Thr Gln Phe Lys Cys
 115 120 125
 Asn Ser Gly Arg Cys Ile Pro Glu His Trp Thr Cys Asp Gly Asp Asn
 130 135 140
 Asp Cys Gly Asp Tyr Ser Asp Glu Thr His Ala Asn Cys Thr Asn Gln
 145 150 155 160
 Ala Thr Arg Pro Pro Gly Gly Cys His Thr Asp Glu Phe Gln Cys Arg
 165 170 175
 Leu Asp Gly Leu Cys Ile Pro Leu Arg Trp Arg Cys Asp Gly Asp Thr
 180 185 190
 Asp Cys Met Asp Ser Ser Asp Glu Lys Ser Cys Glu Gly Val Thr His
 195 200 205
 Val Cys Asp Pro Ser Val Lys Phe Gly Cys Lys Asp Ser Ala Arg Cys
 210 215 220
 Ile Ser Lys Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Asn
 225 230 235 240
 Ser Asp Glu Glu Asn Cys Glu Ser Leu Ala Cys Arg Pro Pro Ser His
 245 250 255
 Pro Cys Ala Asn Asn Thr Ser Val Cys Leu Pro Pro Asp Lys Leu Cys
 260 265 270
 Asp Gly Asn Asp Asp Cys Gly Asp Gly Ser Asp Glu Gly Glu Leu Cys
 275 280 285
 Asp

<210> 36
 <211> 40
 <212> PRT
 <213> Homo sapiens

<400> 36
 Thr Cys Pro Pro Asn Gln Phe Ser Cys Ala Ser Gly Arg Cys Ile Pro
 1 5 10 15
 Ile Ser Trp Thr Cys Asp Leu Asp Asp Asp Cys Gly Asp Arg Ser Asp
 20 25 30
 Glu Ser Ala Ser Cys Ala Tyr Pro
 35 40

<210> 37
 <211> 79
 <212> PRT
 <213> Homo sapiens

<400> 37
 Thr Cys Pro Pro Asn Gln Phe Ser Cys Ala Ser Gly Arg Cys Ile Pro
 1 5 10 15
 Ile Ser Trp Thr Cys Asp Leu Asp Asp Asp Cys Gly Asp Arg Ser Asp
 20 25 30
 Glu Ser Ala Ser Cys Ala Tyr Pro Thr Cys Phe Pro Leu Thr Gln Phe
 35 40 45
 Thr Cys Asn Asn Gly Arg Cys Ile Asn Ile Asn Trp Arg Cys Asp Asn
 50 55 60
 Asp Asn Asp Cys Gly Asp Asn Ser Asp Glu Ala Gly Cys Ser His
 65 70 75

<210> 38
 <211> 126
 <212> PRT
 <213> Homo sapiens

<400> 38
 Thr Cys Pro Pro Asn Gln Phe Ser Cys Ala Ser Gly Arg Cys Ile Pro
 1 5 10 15
 Ile Ser Trp Thr Cys Asp Leu Asp Asp Asp Cys Gly Asp Arg Ser Asp
 20 25 30
 Glu Ser Ala Ser Cys Ala Tyr Pro Thr Cys Phe Pro Leu Thr Gln Phe
 35 40 45
 Thr Cys Asn Asn Gly Arg Cys Ile Asn Ile Asn Trp Arg Cys Asp Asn
 50 55 60
 Asp Asn Asp Cys Gly Asp Asn Ser Asp Glu Ala Gly Cys Ser His Ser
 65 70 75 80
 Cys Ser Ser Thr Gln Phe Lys Cys Asn Ser Gly Arg Cys Ile Pro Glu
 85 90 95
 His Trp Thr Cys Asp Gly Asp Asn Asp Cys Gly Asp Tyr Ser Asp Glu
 100 105 110
 Thr His Ala Asn Cys Thr Asn Gln Ala Thr Arg Pro Pro Gly
 115 120 125

<210> 39
 <211> 68
 <212> PRT

<213> Homo sapiens

<400> 39
Thr Cys Pro Pro Asn Gln Phe Ser Cys Ala Ser Gly Arg Cys Ile Pro
1 5 10 15
Ile Ser Trp Thr Cys Asp Leu Asp Asp Asp Cys Gly Asp Arg Ser Asp
20 25 30
Glu Ser Ala Ser Cys Ala Tyr Pro Thr Cys Phe Pro Leu Thr Gln Phe
35 40 45
Thr Cys Asn Asn Gly Arg Cys Ile Asn Ile Asn Trp Arg Cys Asp Asn
50 55 60
Asp Asn Asp Cys
65

<210> 40
<211> 248
<212> PRT
<213> Homo sapiens

<400> 40
Cys Pro Pro Asn Gln Phe Ser Cys Ala Ser Gly Arg Cys Ile Pro Ile
1 5 10 15
Ser Trp Thr Cys Asp Leu Asp Asp Asp Cys Gly Asp Arg Ser Asp Glu
20 25 30
Ser Ala Ser Cys Ala Tyr Pro Thr Cys Phe Pro Leu Thr Gln Phe Thr
35 40 45
Cys Asn Asn Gly Arg Cys Ile Asn Ile Asn Trp Arg Cys Asp Asn Asp
50 55 60
Asn Asp Cys Gly Asp Asn Ser Asp Glu Ala Gly Cys Ser His Ser Cys
65 70 75 80
Ser Ser Thr Gln Phe Lys Cys Asn Ser Gly Arg Cys Ile Pro Glu His
85 90 95
Trp Thr Cys Asp Gly Asp Asn Asp Cys Gly Asp Tyr Ser Asp Glu Thr
100 105 110
His Ala Asn Cys Thr Asn Gln Ala Thr Arg Pro Pro Gly Gly Cys His
115 120 125
Thr Asp Glu Phe Gln Cys Arg Leu Asp Gly Leu Cys Ile Pro Leu Arg
130 135 140
Trp Arg Cys Asp Gly Asp Thr Asp Cys Met Asp Ser Ser Asp Glu Lys
145 150 155 160
Ser Cys Glu Gly Val Thr His Val Cys Asp Pro Ser Val Lys Phe Gly
165 170 175
Cys Lys Asp Ser Ala Arg Cys Ile Ser Lys Ala Trp Val Cys Asp Gly
180 185 190
Asp Asn Asp Cys Glu Asp Asn Ser Asp Glu Glu Asn Cys Glu Ser Leu
195 200 205
Ala Cys Arg Pro Pro Ser His Pro Cys Ala Asn Asn Thr Ser Val Cys
210 215 220
Leu Pro Pro Asp Lys Leu Cys Asp Gly Asn Asp Asp Cys Gly Asp Gly
225 230 235 240
Ser Asp Glu Gly Glu Leu Cys Asp
245

<210> 41
<211> 39
<212> PRT
<213> Homo sapiens

<400> 41
 Thr Cys Phe Pro Leu Thr Gln Phe Thr Cys Asn Asn Gly Arg Cys Ile
 1 5 10 15
 Asn Ile Asn Trp Arg Cys Asp Asn Asp Asn Asp Cys Gly Asp Asn Ser
 20 25 30
 Asp Glu Ala Gly Cys Ser His
 35

<210> 42
 <211> 86
 <212> PRT
 <213> Homo sapiens

<400> 42
 Thr Cys Phe Pro Leu Thr Gln Phe Thr Cys Asn Asn Gly Arg Cys Ile
 1 5 10 15
 Asn Ile Asn Trp Arg Cys Asp Asn Asp Asn Asp Cys Gly Asp Asn Ser
 20 25 30
 Asp Glu Ala Gly Cys Ser His Ser Cys Ser Ser Thr Gln Phe Lys Cys
 35 40 45
 Asn Ser Gly Arg Cys Ile Pro Glu His Trp Thr Cys Asp Gly Asp Asn
 50 55 60
 Asp Cys Gly Asp Tyr Ser Asp Glu Thr His Ala Asn Cys Thr Asn Gln
 65 70 75 80
 Ala Thr Arg Pro Pro Gly
 85

<210> 43
 <211> 169
 <212> PRT
 <213> Homo sapiens

<400> 43
 Thr Cys Phe Pro Leu Thr Gln Phe Thr Cys Asn Asn Gly Arg Cys Ile
 1 5 10 15
 Asn Ile Asn Trp Arg Cys Asp Asn Asp Asn Asp Cys Gly Asp Asn Ser
 20 25 30
 Asp Glu Ala Gly Cys Ser His Ser Cys Ser Ser Thr Gln Phe Lys Cys
 35 40 45
 Asn Ser Gly Arg Cys Ile Pro Glu His Trp Thr Cys Asp Gly Asp Asn
 50 55 60
 Asp Cys Gly Asp Tyr Ser Asp Glu Thr His Ala Asn Cys Thr Asn Gln
 65 70 75 80
 Ala Thr Arg Pro Pro Gly Gly Cys His Thr Asp Glu Phe Gln Cys Arg
 85 90 95
 Leu Asp Gly Leu Cys Ile Pro Leu Arg Trp Arg Cys Asp Gly Asp Thr
 100 105 110
 Asp Cys Met Asp Ser Ser Asp Glu Lys Ser Cys Glu Gly Val Thr His
 115 120 125
 Val Cys Asp Pro Ser Val Lys Phe Gly Cys Lys Asp Ser Ala Arg Cys
 130 135 140
 Ile Ser Lys Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Asn
 145 150 155 160
 Ser Asp Glu Glu Asn Cys Glu Ser Leu
 165

<210> 44
 <211> 209

<212> PRT

<213> Homo sapiens

<400> 44

Thr Cys Phe Pro Leu Thr Gln Phe Thr Cys Asn Asn Gly Arg Cys Ile
1 5 10 15
Asn Ile Asn Trp Arg Cys Asp Asn Asp Asn Cys Gly Asp Asn Ser
20 25 30
Asp Glu Ala Gly Cys Ser His Ser Cys Ser Ser Thr Gln Phe Lys Cys
35 40 45
Asn Ser Gly Arg Cys Ile Pro Glu His Trp Thr Cys Asp Gly Asp Asn
50 55 60
Asp Cys Gly Asp Tyr Ser Asp Glu Thr His Ala Asn Cys Thr Asn Gln
65 70 75 80
Ala Thr Arg Pro Pro Gly Gly Cys His Thr Asp Glu Phe Gln Cys Arg
85 90 95
Leu Asp Gly Leu Cys Ile Pro Leu Arg Trp Arg Cys Asp Gly Asp Thr
100 105 110
Asp Cys Met Asp Ser Ser Asp Glu Lys Ser Cys Glu Gly Val Thr His
115 120 125
Val Cys Asp Pro Ser Val Lys Phe Gly Cys Lys Asp Ser Ala Arg Cys
130 135 140
Ile Ser Lys Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Asn
145 150 155 160
Ser Asp Glu Glu Asn Cys Glu Ser Leu Ala Cys Arg Pro Pro Ser His
165 170 175
Pro Cys Ala Asn Asn Thr Ser Val Cys Leu Pro Pro Asp Lys Leu Cys
180 185 190
Asp Gly Asn Asp Asp Cys Gly Asp Gly Ser Asp Glu Gly Glu Leu Cys
195 200 205
Asp

<210> 45

<211> 47

<212> PRT

<213> Homo sapiens

<400> 45

Ser Cys Ser Ser Thr Gln Phe Lys Cys Asn Ser Gly Arg Cys Ile Pro
1 5 10 15
Glu His Trp Thr Cys Asp Gly Asp Asn Asp Cys Gly Asp Tyr Ser Asp
20 25 30
Glu Thr His Ala Asn Cys Thr Asn Gln Ala Thr Arg Pro Pro Gly
35 40 45

<210> 46

<211> 89

<212> PRT

<213> Homo sapiens

<400> 46

Ser Cys Ser Ser Thr Gln Phe Lys Cys Asn Ser Gly Arg Cys Ile Pro
1 5 10 15
Glu His Trp Thr Cys Asp Gly Asp Asn Asp Cys Gly Asp Tyr Ser Asp
20 25 30
Glu Thr His Ala Asn Cys Thr Asn Gln Ala Thr Arg Pro Pro Gly Gly
35 40 45

Cys His Thr Asp Glu Phe Gln Cys Arg Leu Asp Gly Leu Cys Ile Pro
50 55 60
Leu Arg Trp Arg Cys Asp Gly Asp Thr Asp Cys Met Asp Ser Ser Asp
65 70 75 80
Glu Lys Ser Cys Glu Gly Val Thr His
85

<210> 47
<211> 170
<212> PRT
<213> Homo sapiens

<400> 47
Ser Cys Ser Ser Thr Gln Phe Lys Cys Asn Ser Gly Arg Cys Ile Pro
1 5 10 15
Glu His Trp Thr Cys Asp Gly Asp Asn Asp Cys Gly Asp Tyr Ser Asp
20 25 30
Glu Thr His Ala Asn Cys Thr Asn Gln Ala Thr Arg Pro Pro Gly Gly
35 40 45
Cys His Thr Asp Glu Phe Gln Cys Arg Leu Asp Gly Leu Cys Ile Pro
50 55 60
Leu Arg Trp Arg Cys Asp Gly Asp Thr Asp Cys Met Asp Ser Ser Asp
65 70 75 80
Glu Lys Ser Cys Glu Gly Val Thr His Val Cys Asp Pro Ser Val Lys
85 90 95
Phe Gly Cys Lys Asp Ser Ala Arg Cys Ile Ser Lys Ala Trp Val Cys
100 105 110
Asp Gly Asp Asn Asp Cys Glu Asp Asn Ser Asp Glu Glu Asn Cys Glu
115 120 125
Ser Leu Ala Cys Arg Pro Pro Ser His Pro Cys Ala Asn Asn Thr Ser
130 135 140
Val Cys Leu Pro Pro Asp Lys Leu Cys Asp Gly Asn Asp Asp Cys Gly
145 150 155 160
Asp Gly Ser Asp Glu Gly Glu Leu Cys Asp
165 170

<210> 48
<211> 42
<212> PRT
<213> Homo sapiens

<400> 48
Gly Cys His Thr Asp Glu Phe Gln Cys Arg Leu Asp Gly Leu Cys Ile
1 5 10 15
Pro Leu Arg Trp Arg Cys Asp Gly Asp Thr Asp Cys Met Asp Ser Ser
20 25 30
Asp Glu Lys Ser Cys Glu Gly Val Thr His
35 40

<210> 49
<211> 83
<212> PRT
<213> Homo sapiens

<400> 49
Gly Cys His Thr Asp Glu Phe Gln Cys Arg Leu Asp Gly Leu Cys Ile
1 5 10 15

Pro Leu Arg Trp Arg Cys Asp Gly Asp Thr Asp Cys Met Asp Ser Ser
20 25 30
Asp Glu Lys Ser Cys Glu Gly Val Thr His Val Cys Asp Pro Ser Val
35 40 45
Lys Phe Gly Cys Lys Asp Ser Ala Arg Cys Ile Ser Lys Ala Trp Val
50 55 60
Cys Asp Gly Asp Asn Asp Cys Glu Asp Asn Ser Asp Glu Glu Asn Cys
65 70 75 80
Glu Ser Leu

<210> 50
<211> 123
<212> PRT
<213> Homo sapiens

<400> 50
Gly Cys His Thr Asp Glu Phe Gln Cys Arg Leu Asp Gly Leu Cys Ile
1 5 10 15
Pro Leu Arg Trp Arg Cys Asp Gly Asp Thr Asp Cys Met Asp Ser Ser
20 25 30
Asp Glu Lys Ser Cys Glu Gly Val Thr His Val Cys Asp Pro Ser Val
35 40 45
Lys Phe Gly Cys Lys Asp Ser Ala Arg Cys Ile Ser Lys Ala Trp Val
50 55 60
Cys Asp Gly Asp Asn Asp Cys Glu Asp Asn Ser Asp Glu Glu Asn Cys
65 70 75 80
Glu Ser Leu Ala Cys Arg Pro Pro Ser His Pro Cys Ala Asn Asn Thr
85 90 95
Ser Val Cys Leu Pro Pro Asp Lys Leu Cys Asp Gly Asn Asp Asp Cys
100 105 110
Gly Asp Gly Ser Asp Glu Gly Glu Leu Cys Asp
115 120

<210> 51
<211> 41
<212> PRT
<213> Homo sapiens

<400> 51
Val Cys Asp Pro Ser Val Lys Phe Gly Cys Lys Asp Ser Ala Arg Cys
1 5 10 15
Ile Ser Lys Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Asn
20 25 30
Ser Asp Glu Glu Asn Cys Glu Ser Leu
35 40

<210> 52
<211> 81
<212> PRT
<213> Homo sapiens

<400> 52
Val Cys Asp Pro Ser Val Lys Phe Gly Cys Lys Asp Ser Ala Arg Cys
1 5 10 15
Ile Ser Lys Ala Trp Val Cys Asp Gly Asp Asn Asp Cys Glu Asp Asn
20 25 30

Ser Asp Glu Glu Asn Cys Glu Ser Leu Ala Cys Arg Pro Pro Ser His
35 40 45
Pro Cys Ala Asn Asn Thr Ser Val Cys Leu Pro Pro Asp Lys Leu Cys
50 55 60
Asp Gly Asn Asp Asp Cys Gly Asp Gly Ser Asp Glu Gly Glu Leu Cys
65 70 75 80
Asp

<210> 53
<211> 40
<212> PRT
<213> Homo sapiens

<400> 53
Ala Cys Arg Pro Pro Ser His Pro Cys Ala Asn Asn Thr Ser Val Cys
1 5 10 15
Leu Pro Pro Asp Lys Leu Cys Asp Gly Asn Asp Asp Cys Gly Asp Gly
20 25 30
Ser Asp Glu Gly Glu Leu Cys Asp
35 40

<210> 54
<211> 10
<212> PRT
<213> Homo sapiens

<400> 54
Ser Gly Phe Ser Leu Gly Ser Asp Gly Lys
1 5 10
<210> 55
<211> 10
<212> PRT
<213> Homo sapiens

<400> 55
Gly Ile Ala Leu Asp Pro Ala Met Gly Lys
1 5 10
<210> 56
<211> 10
<212> PRT
<213> Homo sapiens

<400> 56
Gly Gly Ala Leu His Ile Tyr His Gln Arg
1 5 10
<210> 57
<211> 11
<212> PRT
<213> Homo sapiens

<400> 57
Val Phe Phe Thr Asp Tyr Gly Gln Ile Pro Lys
1 5 10